

# The woman, patient after WHI

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## Abstract

An epidemic of fear and distrust has infected women (and physicians) after publication of the Women's Health Initiative (WHI). The overinflated negative data emerging from the oestrogenic arm of WHI have frightened women and given rise to the most difficult emotions to cope with. Keywords such as cancer, death and hormones, combined together, have potentiated an avoidant attitude towards hormonal therapy (HT) driven more emotionally than rationally. This negative aura has not been dissipated by the positive data from the oestrogen-only arm of WHI.

This paper will discuss: women's different emotional reactions to and coping strategies for HT-related fear after WHI; the communication skills physicians should use in focusing on positive messages emerging from WHI; predictors of current HT use; the meaning of the higher use of HT in postmenopausal highly-educated women and women gynaecologists; the importance of increasing healthy life-styles as a *taking of responsibility towards aging* by every woman; shifting from passivity to active sharing of the decision making process with the caring physician; and the use of an individually tailored HT, when appropriate, as part of an active strategy in the pursuit of a longer *health expectancy*.

## The woman, patient after WHI

Two epidemics have infected women after Women's Health Initiative (WHI) [1-3] publications: the epidemic of fear and the epidemic of distrust. With a variable degree of severity, these infections, metaphorically speaking, have spread among physicians as well, WHI data having exacerbated the concerns previously raised by the Heart and Oestrogen/Progestin Replacement Study (HERS) [4-7].

The debates [6-8] that followed publication of the results from these two large clinical trials have underscored the difficulty of defining the optimal approach for dealing with the symptoms and health changes associated with menopause. The Million Women Study (MWS) [9], in spite of its lower level of evidence (II-2) compared to the WHI (I) and HERS (I), further fuelled fear by the extensive negative media coverage it generated.

The inaccurate, emotional and somewhat arrogant editorial that accompanied the MWS publication increased both fear and distrust, suggesting that physicians have vested interests and that hormone therapy is a "new development" [10]. Reactions to the findings of the studies have dramatically illustrated the uncertainty and the emotional vulnerability of the medical profession regarding the usefulness and even the safety of Hormonal Therapy (HT). They further contribute to maintaining the negative emotions raised by these studies and increase the difficulty of the woman's and physician's decision making process, in spite of the publication of very balanced editorials on WHI and MWS [11-13], on the primary role of oestrogens in relieving acute vasomotor symptoms [14], and of authoritative position statements [15-17]. More recently, a new study has confirmed the difficulties in the therapeutic decision in menopause [18] to treat the relatively heavy burden of symptoms, reported as high as 60% (sleep disturbances) or 58% (hot flashes) even in healthy middle-upper class women, usually considered less vulnerable to menopausal symptoms and complaints.

The huge effort to put the recent WHI data into perspective after more than 50 years of research on HT—that is, not to throw away the baby with the bath water—has only partially succeeded. Many women and physicians are still trapped in

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fear and distrust. Yet at least 30% of postmenopausal women do need HT to improve their symptoms and their overall quality of life [13].

Prescription tracking in the last four years indicates two major trends in the curve of HT selling, which mirror parallel fears and behaviours in women and physicians (fig 1). The first is the fall in prescriptions, which began insidiously after the HERS publication and dramatically accelerated after July 8<sup>th</sup>, 2002, until the late spring of 2003. The second is the current stabilization of HT prescriptions with some minor fluctuations, forming a substantial plateau. The only exception is Tibolone, which in Europe is experiencing a stronger positive trend in the second half of 2004.

How do women (and physicians) cope with the complex emotions they feel when confronted with the potential health risks associated with HT? This key aspect of the problem has been almost neglected in the scientific literature. Most of the excellent papers and comments after WHI have been devoted to discussions of: a) the negative results of the study in terms of disease prevention [1-8]; b) analyses of the study's weaknesses [11-13, 19,20]; and c) the different characteristics of women really attending menopause clinics in Europe in comparison to those involved in the American study [17].

A different view, centred on the woman's perspective after WHI will be discussed here. The emotional behaviour after WHI, the coping strategies of women (but also of physicians), and the identity of the woman who is using and will use HT in spite of WHI will be analysed. The aim is to contribute to a better understanding of: a) how the decision making process on HT is influenced by negative emotions such as fear; b) who are the women more vulnerable to its negative effects; c) what are the predictors of HT use in spite of WHI results; and d) what could be the positive coping and communication strategies for reaching a woman-centred serene awareness about the possible use of HT.

### The epidemics of fear and distrust

Fear, with its immediate biological correlate, anxiety, is one the most infectious basic emotional command-systems [21,22]. It may be triggered by threats as well as by real events. It spreads rapidly among humans through verbal and non-verbal mechanisms, particularly when the perception of its real meaning is over-inflated by mediagenic terrorism. It has a right of precedence over any other emotion or thought because it drives the acute survival-related mechanisms. The key mediator is *adrenaline*. On the perceptual side the leading feeling is *fear-anxiety*, on the motor side it is the "*flight*" response, where the animal or human rapidly runs away and try to hide [21,22]. In the nervous system, fear activates three major pathways: the autonomic system, the intensity of neurovegetative reactions being proportional to the *perceived* severity of the feared/threatening stimulus; the emotional-affective system; and the cognitive system. The behavioural and clinical correlates of fear are the tip of the iceberg of very complex changes in neuro and psychoplasticity within the brain. For example, the flight response is physical in an animal, but may be physical or symbolic in human beings, in whom motor actions correlated to fears are often socially inhibited. *Avoidance* of frightening behaviours or situations, and/or giving-up the feared choices is a frequent human expression of fear [22]. Quite interestingly, anxiety disorders are more prevalent in women, with a ratio up of 3:1 in transitional periods (adolescence and perimenopause) when higher fluctuations of oestrogen plasma levels may destabilize the hypothalamic adrenergic set-point, increasing women's vulnerability to anxiety triggering factors.

When acute, fear bypasses the cognitive judgment and blunts cultural and socioeconomic differences. When chronic, cultural skills do make a difference in the choice and efficacy of coping strategies. This fact will be discussed in its full meaning here when considering HT's choice in women physicians.

After WHI, fear of HT was triggered through two major exogenous frightening stimuli:

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- a) the “mediagenic” (expression coined by AG) emphasis given to the negative data. Titles or texts such as “Hormones increase breast cancer by thirty per cent after the menopause”, “Drug companies are poisoning women only to make profits”, “Physicians are ‘virtually abusing’ women by prescribing dangerous hormones”, “Physicians are sold to drug companies”, or “Physician have vested interests” have urged women to seriously reconsider their HT after the menopause. Many women felt betrayed. The distrust peaked. Questions and comments such as: “How could my physician have prescribed hormones to me, knowing that they are so dangerous?” or “I cannot trust my physician any more” have been heard in radio and TV programs and read in letters to women's and health magazines;
- b) the “iatrogenic” factor. Instead of keeping calm and discussing the positive lessons given by WHI and the Million Women Study, the vast majority of physicians panicked. The drop in prescriptions indicates that fear was shared in the medical community as well. Physicians more scared after WHI are those who do not have a personal solid clinical experience with menopausal women and their treatment. The most experienced tried to contain the panic [11-16, 19-20]. Before WHI, many family physicians used to refer women to menopause clinics to start HT. Now, most of them frankly tell the woman that they do not agree with that prescription anymore, or refer women to the very same clinic to give up HT and be consulted and prescribed non hormonal drugs to manage their symptoms. Fear of legal risks further prevents many physicians from reconsidering HT in their practice.

### Fear: the coping strategies

Fear triggered by WHI impacts differently on a woman's internal psychic scenario and final decision making process according to a number of variables—psychological, medical, socioeconomic and cultural. Soon after the WHI release, women's strategies for coping with fear presented a wide spectrum: outburst of anxiety at the beginning, with many “acting-out” their anxiety through suddenly dropping out of HT; avoidance of any other thing labelled as “hormone”... unless “natural”; anger at feeling manipulated or “betrayed”; denial, and rationalisation. At the opposite end, there was the most positive coping, the constructive/cognitive approach, exemplified in: “I want to understand more to make my own decision”, which seems to be currently increasing in parallel with the most acute and confused emotions, particularly in younger, symptomatic and most educated women.

Physicians, on their side, have had their own spectrum of coping strategies after the acute fear and panic soon after the WHI release, that was re-activated in further worrying papers, such as that on worsening risks of Alzheimer's [23]. Interest in “natural” treatment, phytoestrogens first, increased among physicians as well, together with other coping mechanisms such as denial or rationalisation. The constructive/scientific approach was mirrored in the increasing number of papers questioning the conclusions derived from WHI and MWS [11-13, 19,20] and in the effort to publish a balanced position statement [15-17]. This is much needed in the scientific world to help physicians put the WHI results in perspective, to understand the biases in the inclusion criteria [19], baseline monitoring [19], statistical analysis [20] and overall clinical approach to patient selection and primary end-points [11,12,19,20], in spite of a design that is considered the gold standard of clinical research.

However, is this a winning strategy from the perspective of effective management of women's fear? Does this detailed and sophisticated scientific reasoning really help the process of positive coping with women's anxiety? No, unfortunately it does not.

When the driving emotion is fear, the strategic response to cope with it should be emotional as well: simple, positive, reassuring messages (based on solid scientific reasoning, of course). After decades of celebrating prospective randomised placebo-controlled trials as the gold standard of clinical research, questioning the design or the study's

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weaknesses because we do not “like” the result is somewhat a losing strategy, at least from the communication point of view. For the many scared by the data, it looks like a desperate defence, from a losing position.

Why not pursue a strategy of positive coping with fears? This is mandatory particularly when the results are discussed with women, with journalists, and with physicians not trained or expert in the management of menopause.

### Positive communication of study results

On the positive side, WHI (and HERS) results show that:

- a) those who should *not* be treated with HT include obese women (BMI of 30 or more); women with high cardiovascular risk or previous coronary events; and the elderly, unless severely symptomatic and not responsive to non-hormonal treatments;
- b) the *best candidates* for HT are early postmenopausal symptomatic women, more so when they have healthy life-styles.

This is exactly what the majority of physicians do in European countries: they treat early symptomatic women and recommend healthy life-styles [16-17]. This would be very reassuring to women who are consulting a physician for symptom control in the perimenopausal years.

What else should be stressed in the clinical consultation, or when talking with journalists? First, the risk of breast, endometrial, colorectal, liver and pancreatic cancer increases significantly with increasing body weight (more appropriately, BMI in medical terms) [24]. Second, both for the *breast* and the *endometrium* the *cancer risk associated with elevated body weight (BMI)* [24] *is higher than that with any HT, of any length.* Third, the relative risk (RR) of total mortality diminishes significantly with increasing frequency of physical activity (up to RR=0.58 for four times/week), as indicated in the study on 40,417 postmenopausal women [25]. This strongly supports the importance of a healthy life-style and should be used as a cornerstone in the *taking of responsibility towards ageing* by every woman. Indeed the best synergy is that of regular exercise, adequate body weight *and* appropriate HT to treat acute postmenopausal symptoms, when indicated, and to pursue a longer *health expectancy*.

Moreover:

- a) medroxyprogesterone acetate is not the progestogen of choice, given its mineralcorticoid activity [26-28] that may worsen/precipitate cardiovascular risk, particularly in high-risk subjects;
- b) conjugated oestrogens, when used alone in oestrogen therapy (ET), do not show an increase in breast cancer risk [29]. The WHI oestrogen-only arm, with its less than 7/10,000 invasive breast cancers in comparison to controls [29], questions the initiating role of oestrogens alone in the carcinogenic process and also puts under scrutiny their role in promoting pre-existing precancerous cells. The excess of 8/10,000 breast cancers in the oestrogen+medroxyprogesterone acetate arm [2] questions therefore this specific progestinic component of the treatment *per se*, and/or its interaction with conjugated oestrogens.

If the focus is on the progestinic component of HT, how can we translate it into simple words for women, the media and physicians not skilled in HT?

The endocrine and metabolic action of progestogens (26,27) depends on two major factors: 1) their structure and origin from either progesterone or 19 nor-testosterone; 2) their type of interaction with hormonal receptors [26,27]. Progestogens do not simply interact with the progestinic receptors. They may interact with the oestrogenic, androgenic, glucocorticoid and mineralcorticoid receptors as well [26,27], the final metabolic/endocrine action being the result of this complex interplay. In choosing the optimal progestogens, the goal of this component of the treatment should be considered carefully. If an antiandrogenic action is desired because the woman complains of hair loss, acne or

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hypertrichosis, then cyproterone acetate or drospirenone are the progestogens of choice. If a neutral action is preferred, then natural progesterone or dydrogesterone are the first to be considered. If a very effective endometrial protection with optimal bleeding control is to be obtained with minimal metabolic impact, then nomegestrol acetate is preferred. Finally, if a positive action on sexual desire, physical fitness, assertiveness, mood control and mental energy is desired, then noretisterone, with its stronger androgenic profile, is the progestogen of first choice. Stressing that this is a tailored, clinically oriented choice to best fit the woman's need and not a "try this" casual prescription, is key to giving a sense of a well thought-out, competent and reassuring clinical evaluation.

To cope positively with fears resulting from WHI, we should therefore stress that:

- a) young symptomatic perimenopausal women experience the highest benefit from HT, with minimal risks [15-17];
- b) the small negative results with one very specific drug do not mean that all the other drugs used to treat the same problem should be thrown in the rubbish bin;
- c) the choice of progestogen [26-28] should be made according to the desired biological effect, to provide a satisfying, individually tailored treatment;
- d) the results of the oestrogen-only arm are extremely reassuring when breast cancer risk is considered [12, 28];
- e) the benefits of reduction in bone fractures [7] and reduction of colon cancer risk [1], constantly found in observational studies, are confirmed by WHI as well.

On the positive side, the Million Women Study [9] suggests that:

- 1) whatever the length of previous HT, the increase in breast cancer risk does not persist after withdrawal from treatment, which again questions both the initiating and promoting roles of oestrogen;
- 2) vaginal treatment is safe, i.e., is not associated with increased risk of breast cancer, whatever the type of oestrogen used (RR=0.67, CI 0.30-1.13). The consensus on this point from different prospective studies [30-32] and the positive impact of vaginal oestrogen treatment on urogenital symptoms [30-33] should induce the physician to use this option confidently. This is of the highest importance in women with premature menopause [34], as the distress associated with sexual dysfunction has been shown to be inversely correlated with age: the younger the woman, the higher the distress, which peaks in iatrogenic premature menopause [35]. It is also key in elderly patients, for whom local vaginal treatment may be considered the first choice to address urogenital and sexual symptoms effectively and safely. Obviously, pre-treatment monitoring of the endometrium is recommended in the presence of endometrial risk factors, such as an elevated BMI pre-existing and independent of the vaginal oestrogen treatment;
- 3) whatever the length of previous use of hormonal contraceptives, there is no increase of breast cancer risk [9]. This point addresses a question frequently raised by women when consulting on menopausal symptoms: "I've taken the pill for five (or ten years or more): will this increase my cancer risk if I take hormones for the menopause?" Again, data from the Million Women Study are very reassuring. This further supports the results of the CASH [36] and CARE [37] studies on oral contraceptives and breast cancer risk, indicating no increase of risk even in the subset of women with strong hereditary risk. The more the physician is confident about the HT prescription and the rationale for its use, the more his/her nonverbal language will reassure the woman. The physician's attitude toward HT was reported as the second major factor affecting compliance, after side effects, in a study on drop-outs from HT before WHI [38]. Indeed, the patient is always screening our nonverbal behaviour. In this sense she is "supervising" us: the way we cope with our fears and uncertainties is powerfully captured, consciously and unconsciously, through nonverbal language. The more serene, confident and competent we are, the greater and more reassuring will be the internal coherence the woman perceives between what we verbally say and what we express nonverbally, through our blinking, facial mimicking, postural changes or signs of irritation or uneasiness.

## Predictors of HT use after WHI

The flat (plateau) part of the current HT prescription/selling curve is composite (fig.1). Contributors are: a) women who continued HT in spite of WHI; and b) new entries. This Author's hypothesis is that women in the "flat" zone of the prescription graphic are increasingly different from those who used HT before WHI. A gradual increase is expected in the percentage of young and heavily symptomatic women, who desperately need HT to relieve their symptoms, with a reduction of those who use it as a preventive for cardiovascular disease or Alzheimer's. Can we identify the subsets of women who are using and will use HT? Do we have reliable predictors for who they are?

Brennan et al. [39] recently published their cross-sectional study on 3,673 women aged 40 or older, examined between 1988 and 1994, on health behaviour and menopause. *Predictors of current use* of HT were: higher socioeconomic status and higher education; surgical menopause; younger age; perception of health as good; vitamin intake; awareness of having a high cholesterol level; regular medical care; 5-29 alcoholic drinks per month (from 1/wk to 1/day). In short, HT users led healthier lifestyles. By contrast, predictors of *non-use* were obesity (BMI >30) and physical inactivity, while smoking habits did not seem to affect either choice: a population profile radically different therefore from that of women included in WHI. This huge discrepancy further supports the criticism of WHI's inclusion criteria [19]. Unfortunately, Brennan et al. [39] wrote that: "Some of the apparent benefits of HT found in observational studies may result from healthier or more health conscious women being more likely to choose to take HT (...) *and these differences rather than use of HT may be associated with less disease*" (emphasis added).

Why not consider that the same association may have a quite different meaning: a) HT potentiates the benefit of healthy life styles; b) the benefit is inversely correlated with age—the younger the woman, the higher the benefit; c) negative effects of HT increase with inappropriate life-styles, individual risk factors and age. This is clinically plausible for the very same reason that strenuous exercise potentiates health benefits in healthy people but may precipitate a coronary event in subjects unfit, elderly, obese or with high cardiovascular risk. Again, this provides a simple example adequate when speaking with women or journalists lacking a medical background.

Indeed, consensus exists among epidemiological studies [39-45] in defining predictors of HT use:

- *Age*: the younger the women, the higher the probability that: she will ask for HT, she will be reassured by her physician about the treatment risk/benefit ratio, and positively treated [39-41];
- *Type of menopause*: women who undergo surgical menopause are on average three times more likely to ask for HT and comply with treatment [39-45]. Reasons include: acute perception of what is lost in terms of well-being with the loss of ovarian function, due to the onset of symptoms; having higher expectations in terms of quality of life, body image, sexuality, efficiency, fitness and mental brightness [38]; and perhaps a more acute sense of impairment in comparison to the natural menopause, due both to the sudden changes the woman perceives and the concomitant acute loss of androgens that may worsen the sense of personal impairment [33-35];
- *Higher education and higher income*, which imply increased access to and utilization of high quality health care facilities [39-42, 44-45]. Indeed rich and educated women are more empowered in: a) the negotiation of the consultation time ("I need half an hour as I have many questions to ask you about HT"); b) the choice of the physician ("I want the best in this specialty for my health"); c) request for explanation ("Could you tell me exactly what is my risk of breast [or other] cancer with HT?"); d) sense of personal right to know and skill in getting information (e.g., from the internet); e) attitude in sharing/directing the decision making process.

It is likely that women with these characteristics will increasingly use HT. The higher need for relief of symptoms and higher cognitive skills used in the decision making process enable them to positively cope with fears and distrust, and find a positive equilibrium with a well-tailored HT program as an empowering tool to pursue a longer health expectancy,

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in synergy with a healthier lifestyle. At the opposite end of the spectrum, women with low income, low education, of races other than non-Hispanic white (39,40,44,45), more socially disadvantaged, elderly, or who experience a natural menopause are less likely to use HT after menopause.

### The winning argument against fear

“Women gynaecologists, who know HT, do it”. Indeed, different surveys conducted among women physicians in different countries indicate that among women gynaecologists (but also among wives of male gynaecologists) the rate of HT use is significantly higher than the average use in the same country. It is 7 times higher in Italy: from 8.4% in the general menopausal population to 56.5% in women physicians, to 59% in wives of male gynaecologists [46]. In the most recent published research [46], the median use of HT was 3.7 years. However, 18.5% had used HT for 5 years or more: in this case HT was started significantly earlier than in the other group due to a younger age at menopause. Women physician HT users had a significantly lower body mass index, and more vasomotor and dystrophic symptoms at menopause onset. More women on HT were in good physical health and had an active sex life [46].

In 1998 in Sweden, use of HT was on average 2 times higher among physicians and physician's wives: from 39% in the general population to 72% in women GPs, 87% of gynaecologists' wives and 88% of women gynaecologists, respectively ( $p < 0.01$ ) [47], a finding confirmed in further data analysis [48]. Finally, another US study recently published [49] suggests that current HT use in women MDs is significantly associated ( $p < 0.05$ ) with being younger, sexually active, and an obstetrician-gynaecologist; with having no history of breast cancer, a longer use of oral contraceptives, and being post-hysterectomy. Among premenopausal physicians, intended future HT use was significantly associated with the above-mentioned variables, *plus having more extensive, recent continuing medical education* [49]. If women gynaecologists do it in the vast majority, because they choose the best for their health, why then is this positive attitude not mirrored in the general population? This should be investigated in an appropriately designed study aimed at reducing this therapeutic gap. Attitudes towards HT do indeed make the difference.

### Conclusions

At least 30% of postmenopausal women need HT to relieve their menopausal symptoms. This percentage increases in iatrogenic menopause; the younger the woman, the higher the distress associated with menopausal symptomatology. The epidemic of fear and distrust following HERS, WHI and MWI has frightened women, preventing many of them from using a beneficial treatment to relieve their acute symptoms and improve their quality of life. The most vulnerable to the persistence of fear and the consequent avoidant behaviour towards everything labelled as hormone (unless “natural”) are women with lower education, lower socioeconomic status and of races other than non-Hispanic white. These women particularly need simple reassuring messages to cope with their fears. Women more likely to cope positively with their fears and make a serene and aware choice of HT are those with a higher socioeconomic and cultural status, who feel empowered in their decision making process, more so if younger and after surgical menopause, which further motivates them to ask for help.

Cultural skills are the best way to cope with fears about HT in the long term. This is unequivocally proven by the highest use of HT in menopausal women gynaecologists and wives of male gynaecologists.

HT is not bad *per se*: as for every drug, its use may qualify it as a health enhancer or health damager, according to the indications and contraindications and risk/benefit ratio in the individual woman. The “black and white” dichotomic thinking is typical of simple and/or frightened minds. Frightened physicians and a media focused on scoops have

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potentiated this dangerous (and paranoid) thinking. The mentally skilled and culturally equipped woman and physician overcome the barriers of fear and distrust to get the best for their health.

The sad conclusion is that the worst result of this epidemic of fear and distrust after WHI is to increase the antidemocratic trend of contemporary medicine. Rich and educated women will have the best treatment, inclusive of HT, for relief of their menopausal symptoms.

Why not launch a more positive approach with the simplest and most convincing message: "The vast majority of women gynaecologists personally use HT". This is the simplest, self-explanatory and most reassuring emotional message to use to overcome fear and distrust, in order to help poor and undereducated women reconsider HT, if needed.

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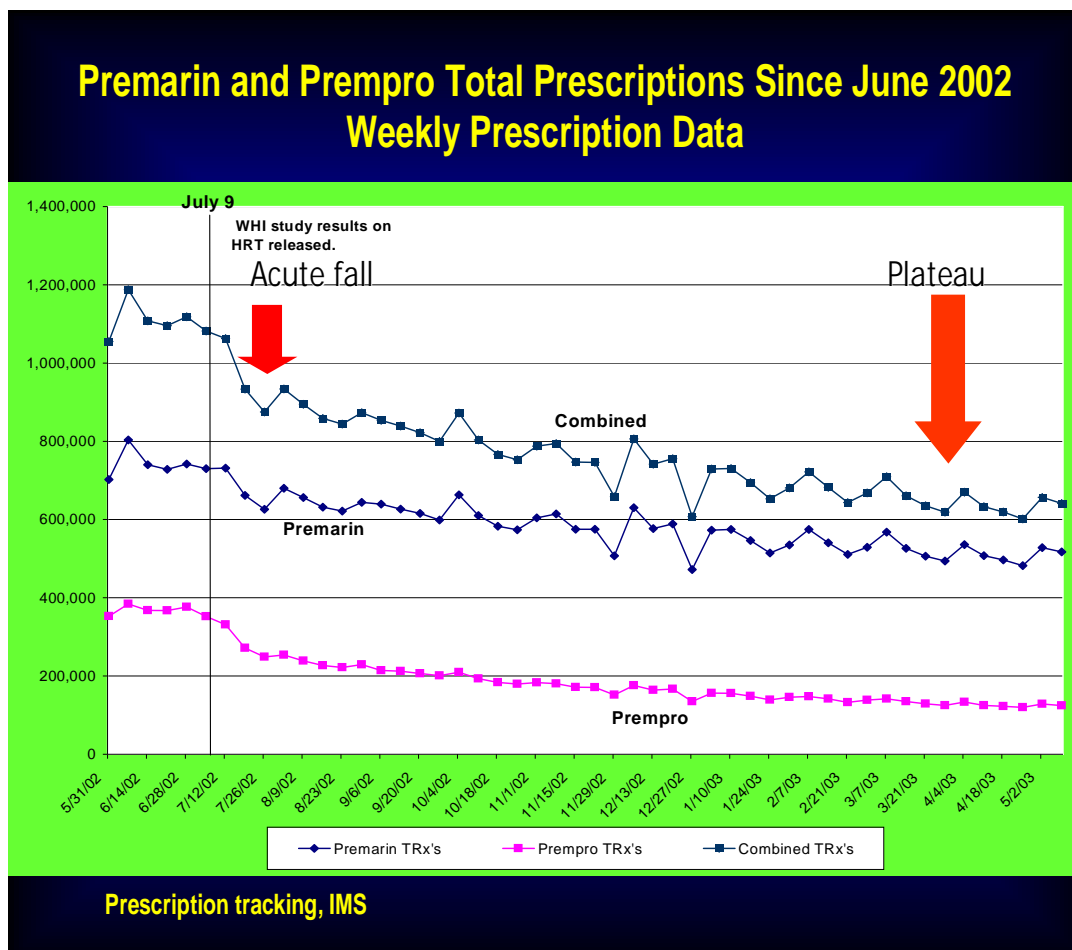


Fig. 1 Prescription tracking indicate two major trends, the rapid fall after July 8th, 2002, and the current plateau. Women on HT in the plateau part of the curve are more likely to be younger, with a iatrogenic menopause, and to have a higher socioeconomic and cultural status than those on HT before WHI release.