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Management of Menopause When Estrogen Cannot Be Used

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Summary

Estrogen deficiency, whether surgically induced or as a consequence of natural ovarian failure, has destructive effects on many organ systems. With current levels of life expectancy, untreated women may expect to spend a third of their lifetime in this state. Appropriate estrogen replacement therapy (ERT) can avert (if started promptly) or ameliorate these devastating consequences, some of which (osteoporotic fractures, increased cardiovascular morbidity) can be lethal. Nevertheless, from 10 to 20% of postmenopausal women may have significant contraindications to ERT. Treatment of symptoms and improving the quality of life is imperative, yet many physicians abjure intervention, for reasons which are not entirely clear. Recent studies of conventional intervention with sedatives or tranquillisers show results equivalent to placebo therapy. On the other hand, specific agents with demonstrated effectiveness are available for management of the major estrogen-deficiency effects, although none of them are truly adequate replacement for the effect of estrogen itself.

There are presently about 40 million women of menopausal age in the United States; it is estimated that this number will grow to 50 million by the turn of the century. Patterns in other developed countries show the same trend. For this large population, the linchpin therapeutic agent for over half a century has been the administration of estrogen in one or other of its forms. Over the past 15 years, 2 problems have constrained global use of estrogen replacement therapy (ERT). One is the issue of noncompliance which, simply stated, is cessation of use of the agent either because of adverse effects or, more often, because of the nuisance of endless monthly withdrawal bleedings inherent in conventional protocols. The other is the ingrained perception of the risk of cancer; this affects not only patients but also, to an unfortunate degree, their treating physicians. These 2 factors compound the problems inherent in dealing with patients with contraindications to estrogen use. Such contraindications, which may include a history of breast or endometrial cancer, active liver disease, or a hormone-related episode of venous thromboembolism, among others, may be considered absolute or merely relative, but they nevertheless present imposing therapeutic dilemmas.

The upshot, in the US, is a situation where no more than 15 to 20% of eligible women ever receive menopausal ERT. Probably less than half of them take the estrogen for any meaningful length of time. The literature seems to indicate that the numbers may even be lower in the United Kingdom.

Solutions to these problems may not be easy. While it is true that education may serve to lessen unreasonable fears concerning estrogen use (although the media will no doubt continue to spread disinformation at intervals), it is still incumbent on clinical investigators to develop therapeutic regimens which eliminate monthly withdrawal bleeding in estrogen/progesterone (progestin) users. An even more difficult challenge is to deal with menopause in women for whom estrogen use is absolutely or strongly contraindicated.

I. Contraindications to Estrogen Use in Menopause

The actual number of women for whom ERT is not an option is hard to estimate, but the magnitude of the problem becomes apparent from a recent prediction of the American Cancer Society that 10% of American women will contract breast cancer in their lifetime and that 1 in 30 women will succumb to it (Silverberg & Lubera 1988). When we add to this rate the other absolute or strong relative contraindications to estrogen use, then the overall rate will increase a few percentage points above 10, and, when one further adds those subjective side effects that may preclude continuation of ERT, then the final percentage of menopausal women for whom estrogen use is not a vi-

Table I. Contraindications to estrogen use

Absolute contraindications
1. Stroke
2. Recent myocardial infarction
3. Breast cancer
4. Endometrial adenocarcinoma
5. Other estrogen-dependent tumours
6. Acute liver diseases
7. Pancreatic disease
8. Gallbladder disease
9. Chronic impaired liver function
10. Recent venous thromboembolic event
11. Chronic thrombophlebitis
12. Undiagnosed vaginal bleeding
Relative contraindications
1. Cigarette smoking/significant nicotine abuse
2. Fibrocystic breast disease
3. Familial hyperlipidaemias
4. Hypertension aggravated by ERT
5. Pancreatitis
6. Hepatic porphyria
7. Endometrial hyperplasia
8. Leiomyomata uteri
9. Endometriosis
10. Migraine headache
Subjective complaints
1. Nausea/gastrointestinal irritation
2. Headaches
3. Breakthrough bleeding
4. Depression
5 Fluid retention

able option may approach 20% (table I). In real numbers this translates to 7 to 10 million women yearly in the US alone.

2. *Traditional Approaches*

Historically, it has been simple to deal with the symptomatic woman for whom ERT was forbidden. Overriding concern for potential propagation of malignancy or recurring thromboses more or less mandated a nihilistic or, at the very least, a minimalistic approach. One simply accepted the unhappy circumstance, resorted to symptomatic treatment of the 'psychological' phenomena, and managed the rest with sympathy and reassurance.

2.1 Traditional Therapies

Traditional therapies have focused on both early and late clinical consequences of the menopause. Earlier, more subjective problems include hot flushes and night sweats, as well as emotional swings, while the later problems of menopause, which may seem to be rather more objective at first, revolve around osteoporosis and cardiovascular changes. Atrophy of the vaginal tissues may present problems throughout postmenopausal life.

2.1.1 Hot Flushes/Night Sweats/Psychological Changes

The most commonly employed agent, where ERT has been contraindicated, has been a combination prescription drug consisting of atropine, ergotamine, and phenobarbital. Although conventional wisdom held this agent to be an excellent substitute for ERT in these circumstances, our own experience, as well as that of others, has yielded different conclusions: there has been little additional success in stemming vasomotor symptoms over what could be expected in any placebo study.

Progesterones, on the other hand, have traditionally been employed to combat hot flushes where estrogen is contraindicated, and their use is generally gratifying (Albrecht et al. 1981; Gambrell Jr 1982; Morrison et al. 1980). Reservations about using one steroid when another has been contraindicated (a rather simplistic misperception) have held back use of progesterones to some degree. This is particularly true in the case of thromboembolic diseases and liver disease.

Many other traditional therapies, including sedatives and tranquillisers, have enjoyed varying degrees of success in the treatment of vasomotor symptoms.

2.1.2 Vaginal Dryness/Dyspareunia

This problem has never been easy to solve, other than on a very short term basis. The use of lubricating agents (most recently water-soluble lubricants) at the time of sexual intercourse is all that has been available. No drug employed as a substitute for estrogen for any particular therapeutic goal

has the ability either to lower the pH of the vagina or to provide long-lasting relief of vaginal symptoms.

2.1.3 Osteoporosis

The traditional approach to osteoporosis when estrogen could not be used has been to employ supportive measures such as exercise protocols and dietary adjustments which include maintenance of proper calcium and vitamin D intake (Ayalon et al. 1987; Goodman 1985; Kroiner et al. 1983; White et al. 1984). Calcium alone will not adequately substitute for estrogen as a first-line agent although proper calcium intake is certainly recommended (Riis et al. 1987). Enthusiasm for both progesterones and androgens is not new, but both have been plagued by other concerns, namely the overlapping of contraindications for estrogens and progesterones, as well as the undesirable adverse effects of prolonged androgen use (Buchanan et al. 1988; Lindsay et al. 1978; Riis et al. 1988).

3. Recent Advances

The most impressive advances in the management of menopause without ERT capitalise on the wealth of clinical investigation in the area of osteoporosis. Numerous newer agents and protocols seem to represent true opportunities. Our own and other investigational experiences with weak estrogenic/antiestrogenic compounds, such as clomifene, in both animals and humans has generated enthusiasm for their potential broad-based use. These compounds appear to exhibit some marked estrogenic properties when endogenous estrogens are lacking, and this may be particularly true in the area of bone metabolism (see section 4.4). We have also found clomifene to exert estrogen-like activity on gonadotrophins and uterine weight in the oophorectomised rat model (Young et al. 1989a), and Still and Greiss (1976) reported similar effects on uterine blood flow in the oophorectomised ewe.

Although we have had a great deal of experience with medications employed to counteract vasomotor instability (table II), none has as yet proved to be as beneficial as estrogen itself. Progesterones appear to come the closest (see section 3.2.5).

3.1 Vaginal Dryness/Dyspareunia

A new development in this area leads us to believe that significant progress may soon be reported. Early studies, in both humans and animals, with a new mucoadherent compound, polycarbophil, show marked improvement over conventional lubricants. This agent is not only longer acting, but, in addition to providing lubrication, appears to be able to lower vaginal pH, thus helping to restore a more normal vaginal milieu. The water-soluble jellies currently prescribed provide some temporary lubrication but are otherwise more messy to use and do not affect pH. Investigation of polycarbophil at our own and other institutions is continuing.

3.2 Vasomotor Symptoms

Evaluation of therapeutic effects on autonomic imbalance continues to suffer from a lack of well-controlled studies. The placebo effect in this situation is well known and it has been difficult to establish just how long it might persist. Consequently, enthusiastic early reports on the efficacy of a great many compounds frequently fail to stand up under longer or more sophisticated scrutiny.

3.2.1 Naproxen

Initial enthusiasm for this compound (Edgren & Morton 1986) was based on a reported 50% reduction in hot flushes, but no placebo group was available for comparison. Currently it is felt that naproxen exerts little more than a placebo effect.

3.2.2 Clonidine

Clonidine has been found to be of some use in countering vasomotor symptoms, especially in women with pre-existing hypertension, for which this α-adrenergic agent is commonly used (Baranowska 1987; Ginsburg & O'Reilly 1987; Laufer et al. 1982; Wren & Brown 1986). Baranowska's study demonstrated a significant decrease in plasma lu-

leinising hormone (LH) concentration 60 minutes after clonidine administration. In addition to a reduction in both amplitude and frequency of LH pulsations, clonidine was felt to influence hot flushes via peripheral vascular effects (Ginsburg & O'Reilly 1987). Unfortunately, some severe adverse effects have been reported in normotensive women, including orthostatic hypotension, fatigue, irritability, headaches, and nausea (Wren & Brown 1986). This may direct the use of this agent toward hypertensive patients. More recent placebo-controlled studies, however, have failed to demonstrate a statistically significant reduction in hot flushes. The most commonly used dose of clonidine is 0.1mg twice daily.

Lofexidine is another α-adrenergic drug which may be useful, although it is commonly associated with drowsiness (Jones et al. 1985).

3.2.3 Veralipride

The efficacy of this antidopaminergic compound has been proven in many clinical studies (Cecco et al. 1980; David et al. 1988; Gicquel 1983; Piccione et al. 1984; Wesel et al. 1984). Total elimination of hot flushes has been found in 60 to 80% of women. Patients remained free of symptoms for up to 3 months following cessation of drug use. Those relieved of vasomotor symptoms also showed significant decreases in serum LH and follicle-stimulating hormone (FSH) levels. Evidence of antidopaminergic activity was apparent in the frequent occurrence of galactorrhoea. This adverse effect, as well as breast tenderness, tended to disappear rapidly after discontinuation of the drug. In a comparison with conjugated estrogen, veralipride proved more effective in relieving the symptoms of severe flushing while estrogen was more effective in suppressing mild to moderate symptoms (Wesel & Bosuma 1983). Suppression lasted for about 3 months, with full return of symptoms in about 6 months. The recommended dose of veralipride is 100 mg/day.

Metoclopramide and sulpiride are additional antidopaminergics with similar pharmacological characteristics.

3.2.4 β-Blockers

Dallera et al. (1986) compared the β-blocker sotalol with the benzodiazepine lorazepam and demonstrated a 62% decrease in hot flushes with the former as against 37% with the latter. However, sotalol was found to be much less effective in treating additional menopausal symptoms such as anxiety and insomnia.

3.2.5 Progesterones

This group of compounds has variously been reported to be as effective as estrogens in relieving hot flushes. Long acting agents such as depo-medroxyprogesterone acetate (DMPA), in doses of 50 to 100mg intramuscularly every 2 to 3 months, and oral progesterones [e.g. medroxyprogesterone acetate (MPA) 20 mg/day] have been found to be equally successful (Gambrell Jr 1982; Morrison et al. 1980). Albrecht et al. (1981) demonstrated in a double-blind, placebo-controlled study that both MPA and placebo reduced hot flushes and temperature elevations, but that MPA elicited a better response. In addition, MPA effectively reduced both the frequency and amplitude of LH pulses and further reduced serum LH levels. In a subsequent study, Lobo et al. (1984) compared conjugated estrogen (CE) with DMPA and found that vasomotor symptoms were decreased in a similar manner in both groups.

3.2.6 Naloxone

Naloxone has had mixed results in the treatment of hot flushes. The usefulness of this opiate receptor agonist is limited by its intravenous route of administration, which renders it of almost no practical value (DeFazio et al. 1984).

3.2.7 Methyldopa

This agent in doses of 250mg twice or 3 times daily has proven highly effective in reducing the symptoms of hot flushes (Nesheim & Saetre 1981).

3.2.8 Clomifene

In our own studies, clomifene, in doses of 12.5 to 25mg daily, generally proved ineffective in relieving hot flushes, while at the same time showing

evidence of other estrogen-like activities. This is consistent with our previous findings of selective estrogenic activity by this family of compounds (Kauppila et al. 1981, 1988). No matter what other effects they might achieve, clomifene and cyclofenil were not found to cause proliferation of the endometrium, a potentially useful characteristic. Tamoxifen has been associated with endometrial hyperplasia and an increased risk of invasive uterine carcinoma (Fornander et al. 1989), and this drug would need further investigation before long term use could be advised.

Some patients on daily doses of clomifene 25 to 50mg did report persistent improvement of symptoms over long periods of time. This study, however, had no matched controls or placebo comparisons and therefore cannot be included in any analyses of results with antiestrogenic compounds. In earlier reports on the use of clomifene as an adjuvant to estrogen, the drug was found to be only minimally inhibitory of the symptomatic relief afforded by the latter. No significant adverse effects have been reported with the use of clomifene under these circumstances.

3.2.9 Org OD 14

This newer compound, Org OD 14 [(7-alpha, 17-alpha)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one], a synthetic steroid with weak estrogenic as well as progestational and androgenic activity, has been extensively tested in Europe. When given orally, usually in doses of 2.5 mg/day, it has been shown to have a beneficial effect on such vasomotor symptoms as hot flushes and increased perspiration. Lindsay et al. (1980) demonstrated a decrease in LH and especially in serum FSH levels with Org OD 14, while the prolactin level remained unaffected. Significantly, adverse effects such as vaginal bleeding or weight gain have not been reported (Kicovic et al. 1982; Lindsay et al. 1980; Nevinny-Stickel 1983; Volpe et al. 1986). Further testing may well bear out the early promise of this drug. As yet, concerns about androgenicity have held back marketing of Org OD 14.

3.2.10 Androgens

Androgens have been proven effective in the therapy of vasomotor symptoms, either in combination with estrogen or alone. When used alone, higher doses may be necessary, increasing the incidence and severity of adverse effects. Danazol, for example, has been shown to be only moderately effective: at a dose of 100 mg/day hot flushes were eliminated in only 50% of women (Foster et al. 1985). These agents may have additional usefulness in relieving symptoms of depression and increasing libido, although reports in this area are either anecdotal or are not prospective and well controlled.

3.2.11 Methyldopa

Methyldopa, an aromatic amino acid decarboxylase inhibitor, has been used by numerous clinicians, including the authors, with satisfactory success in controlling hot flushes. As yet, however, no prospective studies exist to support this effect. Known to reduce tissue concentrations of both indolamines and catecholamines, its effect on hot flushes might be mediated via interference in the metabolic pathways of the latter. We have used methyldopa in doses of 250 to 500 mg/day with no untoward effects in normotensive women.

3.2.12 Others

GnRH agonists and bromocriptine have had little clinical evaluation and deserve only passing mention.

4. Osteoporosis

It is here that the most significant strides have been made. While it is perhaps too optimistic to report that estrogen may be equalled or replaced as the linchpin therapeutic agent for postmenopausal osteoporosis, certain undeniable gains have been made and the absolute indispensability of estrogen is being reassessed (table III). A great deal of controversy still exists in this area, and ongoing studies continue to shed new light, as evidenced, for example, in recently published results with slow-release sodium fluoride (see section 4.3).

4.1 Conventional Measures

As with patients in whom estrogen therapy can be used, it is reasonable to employ all possible sup-

Table II. Nonestrogenic drugs to counter autonomic nervous system symptomatology

1. Sedatives, tranquillisers
2. Nonestrogenic steroid hormones:
   - Progesterones
   - Androgens
   - Synthetic steroids with diverse activities
3. Nonsteroidal anti-inflammatory agents
4. α-Adrenergics
5. Antidopaminergics
6. β-Blockers
7. Opiate receptor agonists
8. Aromatic aminoacid decarboxylase inhibitors
9. Nonsteroidal antiestrogens

portive measures to ensure optimal skeletal protection. These measures include adequate calcium intake, although it must be understood that calcium, by itself, is not a satisfactory alternative modality for dealing with osteoporosis (Riis et al. 1987). Proper diet and a sufficient weight-bearing exercise programme are also mandatory. Caffeine and excessive protein intake must be avoided. Where possible, elimination or sharp curtailment of harmful habits such as smoking or excessive alcohol intake are strongly recommended. Re-evaluation of prescription medication regimens must also be carried out, particularly those involving thyroid therapy or steroid use. Finally, appropriate measures to avoid trauma risk in the elderly must be undertaken. These include proper shoes and clothing, hand rails, and curtailment of such drugs as tranquillisers and sedatives.

4.2 Progesterones

Much has been written about the beneficial effects on osteoporosis of adjunctive progesterones employed in ERT (Barrett-Connor 1986). Progesterones alone, however, have also been shown to be useful therapeutic agents in this area. Progesterones may act by increasing new bone formation rather than by decreasing bone resorption (Lindsay et al. 1978). Synthetic progesterones, nortestosterone derivatives such as norethisterone (norethindrone), stimulate bone formation via androgenic/anabolic effects (Riis et al. 1988). In a 3-month study comparing the effects of conjugated estrogens and medroxyprogesterone acetate on postmenopausal women, Lobo et al. (1984) demonstrated reduced urinary calcium/creatinine and hydroxyproline/creatinine ratios in both groups. Results were comparable to ratios found in premenopausal controls, suggesting that both drugs prevented bone resorption. Standard doses for progestational agents have been recommended. Medroxyprogesterone acetate may be used in daily doses of 5 to 20mg, and the depot form in 100 to 200mg doses every 2 to 3 months. More recently, concern has been expressed over the issue of progesterone effects on the lipid profile in menopausal women. As this warrants consideration even in the presence of estrogen replacement, questions will certainly be raised over the use of progesterone alone. Careful epidemiological study is necessary in this area, together with studies of the atherogenic process in women.

4.3 Fluorides

These compounds have been somewhat controversial in the past, due to a purported risk of increased hip fracture related to their use. This was based on reports of nonclastic bone growth stimulated by fluoride use, which led earlier investigators to conclude that while fluorides may have some benefit in preventing trabecular bone fracture (e.g. vertebral bodies), the opposite might be true for cortical bone (Hedlund & Gallagher 1989; Jowsey et al. 1972; Riggs et al. 1987).

Fluorides are essential to the diet and are felt to be required for normal skeletal growth. Studies to prove the usefulness of sodium fluoride in osteoporosis are based on the fact that fluorides stimulate osteoblastic function (Farley et al. 1983). Supplemental vitamin D and calcium have been used in most protocols (Jowsey et al. 1972); calcium may prevent any increase in bone resorption which might occur with fluorides alone.

A recent 5-year study by Pak et al. (1989) demonstrated that cyclic intermittent sodium fluoride in oral doses of 25mg twice daily is of benefit to

Table III. Nonestrogenic drugs to counter development of osteoporosis

1. Calcium/vitamin D
2. Nonestrogenic steroid hormones:
   - Progestagenes
   - Androgens
   - Synthetic steroids with diverse activities
3. Fluoride
4. Nonsteroidal antiestrogens
5. Calcitonin
6. 'Coherence' regimens

patients with osteoporosis. They reported decreased fracture rates and increased presence of newly formed mineralised bone. Adverse effects such as gastrointestinal irritation, always a problem with fluoride use, were avoided through use of a slow-release oral preparation. Calcium and alfacalcidol supplements minimised any potential mineralisation deficit. The intermittent treatment regimen prevented refractoriness. This new formulation is currently awaiting approval in the US.

4.4 Clomifene

When used in primates over a period of time, clomifene decreased urinary loss of calcium (Abbasi & Hodgen 1986). No endometrial proliferation or withdrawal bleeding in response to progesterone was noted. Beall et al. (1984) demonstrated that clomifene protected ovariectomised rats from bone resorption by preventing loss of bone minerals. There was no change in total body calcium. Young et al. (1989b) have shown such beneficial effects of clomifene in menopausal women as decreased urinary hydroxyproline/creatinine ratio. Clomifene did not induce endometrial proliferation in primates, and withdrawal bleeding on exposure to progesterone was absent (Abbasi & Hodgen 1986).

Stewart and Stern (1986) were also able to show that clomifene and a related compound, tamoxifen, were both capable of blocking parathyroid hormone (PTH)-induced bone resorption in an *in vitro* study. In addition, tamoxifen has been shown to block the induction of bone resorption by dinoprostone (prostaglandin E2) and alfacalcidol (Buckley & Goa 1989). This indicates that the mechanism by which antiestrogenic/weak estrogenic compounds act to inhibit resorption was unrelated to the specific agent employed to induce it. Clomifene was used in doses of 12.5 to 25 mg/day.

It is worth noting that this family of compounds is frequently employed in breast cancer therapy, eliminating any need for concern in this area. Properties similar to those we have observed with clomifene have, as might be expected, also been reported with tamoxifen (Turken et al. 1989). Wakley et al. (1988) found that tamoxifen inhibited osteoporosis in rats subjected to unilateral sciatic neurotomy.

4.5 Org OD 14

This new drug, already mentioned in the section on vasomotor symptoms, has also proven to be effective in preventing bone loss at a dose of 2.5 mg/day (Fogelman et al. 1981). It is unlikely to be associated with endometrial hyperplasia or breakthrough bleeding. Decreased alkaline phosphatase activity and urinary hydroxyproline concentration indicate a reduced bone turnover rate. Urinary calcium/creatinine ratios were similar to those achieved with ERT (Lindsay et al. 1980). Multicentre studies suggest that Org OD 14 is as effective as estrogen in preventing bone loss. This is another compound whose selective estrogenicity indicates a potentially high degree of safety.

4.6 Calcitonin

The short term efficacy of this agent, available by intranasal aerosol in Europe and via subcutaneous injection in the United States, has been shown in many studies (MacIntyre et al. 1988; Salvini et al. 1987). The dosage varies, with 20 to 100U up to 3 times weekly having been tried in different protocols. Calcitonin may be particularly useful in dealing with acute focal skeletal pain. Resistance to the drug appears after 12 to 16 months of use. In addition, prolonged use may be associated with anorexia, nausea, and facial flushing.

4.7 Androgens

These drugs are globally anabolic and therefore may have some benefit in the treatment of osteoporosis. Increased levels of endogenous androgens, seen in women with hirsutism, have been associated with increased trabecular bone density, as measured in the lumbar spine (Buchanan et al. 1988). The major drawback to their routine use in menopause continues to be the problem of adverse effects.

4.8 Ergocalciferol

Mild deficiencies in bone loss may be dealt with adequately with ergocalciferol at a dose of 400 μU/day; higher doses may actually induce further bone resorption. The main role of ergocalciferol may be that of an adjuvant.

4.9 Coherence Therapy

Also known as ADFR (activate, depress, free, repeat) or formerly ADPR (P = pause), coherence therapy has been shown to increase trabecular bone mass. Various regimens are offered, for example oral phosphate or PTH to promote bone turnover, followed by etidronic acid (etidronate) or calcitonin to depress it, then a free period followed by repetition of the cycle (Rasmussen et al. 1980). Cycles of approximately 3 months are advocated, repeated a few times. The theory is to promote overall synchronous bone remodelling for maximal benefit. This seemingly effective therapy has few adherents as yet (Pacifici et al. 1988).

5. New Ideas About the Issue of Estrogen Contraindication

Of late, considerable debate has arisen over the issue of definitive prohibition of estrogen use in certain clinical situations. Investigators have now published on the use of ERT in cases of endometrial carcinoma (Creasman et al. 1986), and anecdotal reports have begun to filter in on the use of estrogen in women with a prior history of breast cancer. A recent monograph deals with the pros and cons of this particular issue (Mishell 1989).

The most pressing argument for estrogen replacement would seem to be supported by the fact that neither subsequent pregnancy nor continuing ovarian function appear to have any great effect on overall prognosis for recurrence or survival in cases of breast cancer. The opposing view arises from concern over dormant micrometastases and from the frequent finding of long disease-free intervals followed by recurrence. Although this issue itself may seem to be a rather bold departure from traditional views, we believe that there will probably be rethinking and reformulating of ideas and conclusions as data continue to be gathered. Serious questions remain for today's private practitioner, however, particularly the issue of just how many years constitute a reliable disease-free interval. We therefore recommend a conservative but not inflexible attitude toward the problem of estrogen use in breast cancer.

6. Conclusion

Many alternatives to estrogens are available to counteract the consequences of estrogen deprivation in both early and late menopause in situations where ERT is contraindicated. Some of these drugs are selective in their effects, while others mimic to some extent the estrogens' universal impact. Major clinical benefits can accrue from the appropriate use of these agents to suppress symptoms and diminish metabolic consequences of this deficiency state.

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