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Review - Narrative

Pharmacological interactions and menopausal hormone therapy: a review

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Abstract

Importance and Objective: Menopausal hormone therapy (HT) is widely used, and there are several statements of international scientific societies to guide prescribers; however, a summary of existing literature about possible drug interactions with HT does not exist, although many midlife women take medications for other conditions. Therefore, our objective was to create a document that presents and synthesizes the most relevant interactions. The impact of the interaction itself and the number of candidates for HT who are likely to use other treatments are considered based on the best available evidence.

Methods: A systematic review was performed to determine the best evidence of interaction effects on relevant outcomes of interest for decision making. A working framework was developed to formulate explicit and reasoned recommendations according to four predefined categories for coadministration: (1) can be used without expected risks, (2) acceptable use (no evidence of negative interaction), (3) alternative treatment should be considered, and (4) nonuse without express justification. The project protocol was registered in the Open Science Framework platform (doi: 10.17605/OSF.IO/J6WBC) and in PROSPERO (registration number CRD42020166658).

Results: Studies targeting our objective are scarce, but 23 pharmacological groups were assigned to one of the predefined categories of recommendation for concomitant use of HT. Vaginal HT was assigned to category 1 for 21 of the analyzed pharmacological groups. For oral and transdermal HT (estrogen-only or combined) and tibolone, there were 12 pharmacological groups assigned to category 1, 12 to category 2, 5 to category 3, and 4 to category 4. Results are shown in crossed-tables that are useful for counseling and prescription.

Discussion and conclusions: Available evidence of HT interactions with other drugs is scarce and mainly indirect. It comes from biological plausibility, knowledge of extensive concomitant use without reported incidents, and/or extrapolation from hormonal contraception, but there are pharmacological groups in all categories showing that information is useful. These eligibility criteria summarize it and can help in the decision process of HT coadministration with other drugs. Decisions should be taken based on these recommendations but also individualized risk/benefit evaluation, according to underlying pathology, patient's clinical requirements, and the existence or nonexistence of alternatives.

Key Words: Biological plausibility – Coadministration drugs – Medical eligibility criteria – Menopausal hormone therapy – Pharmacological interactions.

Menopausal hormone therapy (HT) could be used to improve health-related quality of life in perimenopausal and postmenopausal women[1-3] according to the statements of international scientific societies.[4-6] Many midlife women are taking or will take medications for other conditions when HT is recommended; however, data about possible interactions are scarce. In the case of hormonal contraceptive (HC) prescription, the World Health Organization medical eligibility criteria

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classify the medical conditions of women into four categories, providing the clinical community recommendations for the safe use of any contraceptive method,[7] but this has not yet been done for HT. Therefore, the aim of this research project was to define a set of eligibility criteria for using HT in perimenopausal and postmenopausal women concomitantly with different types of treatments of pathological conditions, according to the safety of the treatment. The objective of the study was to create a document that presents and synthesizes in a simple way the most relevant interactions due to the impact of the interaction itself and the number of candidates for HT who are likely to use a certain treatment, all based on best available evidence.

METHODS

A systematic review of the literature was performed, and a working framework was developed to formulate explicit and reasoned recommendations. The study was registered in PROSPERO (registration number CRD42020166658) and is part of the "Eligibility criteria for HT project" whose objectives and methodology (systematic reviews for the definition of HT eligibility criteria) were previously described.[8]

Selection of studies

An exhaustive literature search was conducted in the following databases: MEDLINE (via PubMed), The Cochrane Library (CENTRAL), and EMBASE (via embase.com), from their inception until June 2022. A search strategy was designed tailored to the requirements of each database, which included a combination of controlled vocabulary and search terms related to pharmacological interactions and HT (Supplemental File, http://links.lww.com/MENO/B149), restricted to English and Spanish languages. The PICOS (Population, Intervention, Comparators, Outcomes, Study Design) criteria were developed a priori to guide the scope of the review, along with the procedures, selection, and synthesis of the literature search. The selection criteria were as follows: (Population) perimenopausal and postmenopausal women receiving HT; (Intervention) any HT preparation (estrogens alone or combined with a progestogen, tibolone, or tissue-selective estrogen complex) or any route of administration (oral, transdermal, vaginal, or intranasal), (Outcome) increase/decrease HT effect or drug effect, and (Study Design) randomized controlled trials and related extension studies or follow-up reports. Any complete article that was found to be related to our purpose was reviewed in detail.

Assignment of eligibility criteria

The assignment of recommendation of eligibility for the joint use of drugs that is shown is the result of the combination of the available evidence on interactions of HT with the other treatment to be considered, together with the degree of preference of recommendation that should be had when the clinician proposes its coadministration.

The assignment was made by the "HT Eligibility Criteria Group" in accordance with the following criteria:

Category 1: Coadministration can be used preferentially or without expected risk. This recommendation may come from the existence of high-quality published evidence that supports it (targeted research with conclusive results), and/or more often from the known fact of its wide joint use in the absence of evidence of risks or biological plausibility suggesting risk.

Category 2: High-quality published evidence was not found, but coadministration is considered acceptable by the absence of evidence of negative interaction, or because it is insignificant and the benefit justifies treatment, or because a simple dose adjustment of one or another treatment resolves the incidence.

Category 3: Alternative treatment should be considered, but coadministration is accepted when the benefit outweighs the foreseeable risk of the interaction. This category may also be assigned when the clinical indication for the use of other medication itself poses a certain degree of risk to the use of HT, but in some cases, its use may be justified.

Category 4: Coadministration should not be used without express justification. This recommendation may come from evidence against use, or from the absence of justification for the concomitant treatment due to the plausibility of the undesirable effect of the interaction and/or because the underlying pathology so advises.

When differences of opinion were present among members of the HT Eligibility Criteria Group, the assignment was decided by vote. In addition, a call to the corresponding explanation that motivated the assignment accompanies it when appropriate.

RESULTS

The joint administration of drugs with HT in midlife women is common and generates the possibility of pharmacokinetic interaction (either increasing or decreasing the effect of the drug or the effect of HT). This interaction differs according to the composition, dose, and route of administration of HT. Actually, few quality studies whose aim was similar to our objective have been found, and few provide useful evidence. Therefore, interpretations come from basic studies or from extrapolation of the effects of hormonal contraception (HC). For many drugs, there is, however, extensive population evidence of concomitant use without negative interactions reported, and this is helpful, so it was considered for the assignment.

The results of drug interactions with HT are shown in Tables 1, 2, and 3.[9-105]

The most frequent pharmacological groups were crossed with EPT (combined HT: estroprogestogen, oral and transdermal), ET (estrogens only, oral and transdermal), tissue selective estrogen complex, and tibolone, to create a useful table to guide the prescription, which constitutes the main result of this work.

Some preliminary considerations that must be kept in mind for the interpretation and use of this HT eligibility criteria table based on coadministration with other treatments are discussed hereinafter.

In HT, many different preparations (synthetic and/or natural) with different composition, route of administration, and dose are used, and all imply differences in the pharmacological interactions that one or the other can cause with respect to the same type of associated drug. This variation is more relevant if it is considered that some are used alone or with different progestogens with relevant differences among them. For this reason, within each section, a mention of the peculiarities regarding the routes or doses

TABLE 1. *Pharmacological interactions with commonly used drugs and MHT*

Pharmacological interactions	ET	Estrogens plus progestogens, oral (HT)	Transdermal ET	Transdermal estrogens plus progestogens (HT)	Tibolone	Vaginal HT
Antihypertensive[a]	2 In some patients, probably with some idiosyncrasy, ET may alter blood pressure control and require dose adjustment and confirm that it resolves.	1-2 Clinical trials have shown that when it includes drospirenone (an aldosterone antagonist gestagen), blood pressure is slightly reduced compared with placebo.[9]	1	1	2 In some patients, probably with some idiosyncrasy, tibolone may change blood pressure control and require dose adjustment.[10]	1
Statins[a]	1-2 ET tends to increase triglycerides, total cholesterol, and LDL-cholesterol, and to increase HDL-cholesterol.[11]	1-2 Oral HT tends to increase triglycerides, total cholesterol, and LDL-cholesterol, and to increase HDL-cholesterol.[11]	1-2 Transdermal ET modifies less the lipid profile than oral MHT.[11]	1-2 Transdermal HT modifies the lipid profile less than oral MHT.[11]	1-2 Tibolone may decrease total cholesterol and LDL-cholesterol, but also HDL-cholesterol.[11]	1
Anxiolytics/hypnotics[a] It may be necessary to adjust the dose of benzodiazepines because it could decrease your liver metabolism and increase or decrease the effect. Increased effect of the drug: alprazolam or triazolam. Decreased effect of the drug: lorazepam or tepazepam[12-17]	1	1	1 Transdermal route: no first-pass effect means less probability of interaction with benzodiazepines.	1 Transdermal route: no first-pass effect means less probability of interaction with benzodiazepines.	1-2	1
Analgesics/anti-inflammatory[a]	1 Studies with HC show that oral estrogens can slightly reduce the action of paracetamol because of an increase in its elimination. Also, one study suggested increased estrogenic action. This indirect evidence is considered not very relevant.[18-20]	1 Studies with HC show that oral estrogens can slightly reduce the action of paracetamol due to an increase in its elimination. Also, one study suggested increased estrogenic action. This indirect evidence is considered not very relevant.[18-20]	1	1	1 Studies with HC show that oral estrogens can slightly reduce the action of paracetamol because of an increase in its elimination. Also, one study suggested increased estrogenic action. This indirect evidence is considered not very relevant.[18-20]	1
Antidepressant[a] Most studies with HT and antidepressants show improvement of depression with HT and experiencing climacteric syndrome. If side effects of the antidepressant drug is appreciated, dose adjustment may be required, but this effect is considered insignificant.[21-31]	1	1	1	1	1	1
Thyroid hormones[a]	1-2	1-2	1	1	1-2	1
Oral antidiabetics and insulin HT could slightly modify insulin resistance and slightly improve or worsen control at the start of treatment, especially depending on the progestin, but a simple dose adjustment would solve it.[32,33]	1	1	1	1	1	1

Category 1: can be administered preferentially without inconvenience. Category 2: coadministration is considered acceptable. Category 3: an alternative treatment or review of the indication of HT is recommended, and its use may be justified in some case. Category 4: coadministration should not be used without justification.

ET, estrogen therapy; HC, hormonal contraception; HDL, high-density lipoprotein; HT, hormonal therapy; LDL, low-density lipoprotein; MHT, menopausal hormonal therapy.

[a] The wide experience with the use of these drugs and the lack of adverse effects communicated allow us to consider the probability of no interaction.

TABLE 2. *Other pharmacological interactions with menopausal hormonal therapy (I)*

Pharmacological interactions	ET	Estrogens plus progestogens, oral (HT)	Transdermal ET	Transdermal estrogens plus progestogens (HT)	Tibolone	Vaginal HT
Aromatase inhibitors Subanalyses of clinical trials in women with breast cancer have warned of an increase in recurrences with the association. The biological plausibility of antagonistic effects and the technical data sheets lead to the qualification.[34-37]	4	4	4	4	4	3-4
Bronchodilators[a] In case of oral bronchodilators use, depending on the drug, it may be necessary to adjust dose with oral HT.[38,39]	1-2	1-2	1	1	1-2	1
Anticoagulant[b,40-47]	1-2[b]	1-2 I[b]	1	1	2	1
SERM Use only for approved combinations (conjugated estrogen equine and bazedoxifene [T-SEC]). There is biological plausibility of interaction and unpredictable and potentially undesirable results, so it should not be used.[48]	4 Use only for approved combinations (conjugated estrogen equine y bazedoxifene [T-SEC])	4	4	4	4	3 Data sheet contraindicates its use for women with breast cancer.
Corticosteroids[b] The concomitant use of estrogens could reduce the metabolism of the corticosteroid and it may be necessary to reduce its dose if it is long-term.[49,50]	2	2	2	2	2	1
Antiepileptic Antiepileptic drugs are potent enzyme inducers, making it possible to reduce estrogenic therapeutic effectiveness. Oral HT could reduce the effect of the antiepileptic by interfering with its metabolism.[51-66]	4	4	3-4	3-4	4	1
Enzyme-inhibiting antibiotics (rifampicin, rifabutin) There are no studies on the possible interaction. Presumable interaction in hepatic metabolism that may require dose adjustment.[67-74]	2	2	1	1	2	1
Antineoplastic There are no studies on the possible interaction. Concomitant use not usually required.[75,76]	4	4	4	4	4	1
Immunosuppressant There are no studies on the possible interaction. Dose adjustment may be required.[77,78]	3	3	3	3	3	1

Category 1: can be administered preferentially without inconvenience. Category 2: coadministration is considered acceptable. Category 3: an alternative treatment or review of the indication of HT is recommended, and its use may be justified in some case. Category 4: coadministration should not be used without justification.
ET, estrogen therapy; HT, hormonal therapy; SERM, selective modulator estrogen receptor; T-SEC, tissue selective estrogen complex.
[a]The wide experience with the use of these drugs and the lack of adverse effects communicated allow us to consider the probability of no interaction.
[b]In some women, it may be necessary to adjust the dose of the warfarin anticoagulant, especially at the beginning or change the route of HT administration.

was done when deemed appropriate and/or there is evidence for that. In addition, in some therapeutic groups, the eligibility assignment may include more than one category because of differences within the group, which are explained at the right column of the table.

In many cases, the available evidence on possible HT interactions is limited, but there is evidence for HC. Given the differences between the composition and dose of HT and preparations used in HC, a direct extrapolation of such evidence was not considered acceptable in general. There are, however, some drugs for which the HC information, together with the plausibility for a certain HT interaction, determines their consideration as evidence to influence the eligibility criteria assigned.

In the selective modulator estrogen receptor group, tissue-selective estrogen complex itself constitutes the only acceptable coadministration with high-quality evidence (equine conjugated estrogens with bazedoxifene). Evidence on possible interactions of SERM with the rest of the evaluated drugs was not identified.

Ttibolone, although would be included among progestogens because of its chemical composition, has its own column owing to its characteristic clinical effects that are comparable to EPT and because it has some of its own evidence of possible interactions.

Finally, vaginal HT, at its usual dosage, has local target and action, and some studies have shown that there is no systemic absorption with clinical effects in other areas after 2 weeks of use, and this is supported by clinical experience.

The appropriate different considerations about HT type are included in the tables of eligibility criteria based on the indication that motivated the coadministration of the other drugs.

DISCUSION

The joint administration of drugs with HT in midlife women is common and generates the possibility of pharmacokinetic interaction. Some medical conditions can lead to earlier and more intense menopausal symptoms in women, because of the disease

TABLE 3. *Other pharmacological interactions with menopausal hormonal therapy (II)*

Pharmacological interactions	ET	Estrogens plus progestogens, oral (HT)	Transdermal ET	Transdermal estrogens plus progestogens (HT)	Tibolone	Vaginal HT
Oral antifungal Presumably no relevant interaction in very short-term treatments. No evidence for long-term coadministration [79-86]	1-2 No evidence for long-term coadministration. May require lower dose of ET	1-2 No evidence for long-term coadministration. May require lower dose of HT	1 No evidence for long-term coadministration	1 No evidence for long-term coadministration	1-2 No evidence for long-term coadministration	1
Antiretroviral There are no studies on the possible interaction. It may be necessary to adjust the dose of HT. [87-91]	2	2	2	2	2	1
Dopaminergic There are no studies on the possible interaction. It may be necessary to adjust the dose, especially at the beginning of treatment. With HC, an increase in dopaminergic concentration has been reported. Estrogens can increase the prolactin concentration. [92-95]	2-3	2-3	2-3	2-3	2-3	1
Litholítics There are no studies on the possible interaction. A decrease in the litholytic effect and an increase in hepatic cholesterol have been reported with HC, which could occur with oral MHT. [96,97]	3	3	2	2	3	1
Neurostimulants (caffeine) There are no studies on the possible interaction. The information is indirect evidence that comes from HC studies. No data with HT and it may be enough with the use of lower doses of HT. No effect has been reported in women with high coffee intake.[98-103]	2 Very limited evidence. A single study with ET at high doses for the current use of ET	2	2 Very limited evidence. A single study with ET at high doses for the current use of HT	2	2	1
Antithyroid There are no studies on the possible interaction. Dose adjustment may be required if its use is considered necessary.	2	2	2	2	2	1
Antipsychotics Despite the limited availability of studies, the evidence of wide joint use without associated problems is considered sufficiently relevant for most of them. Concomitant use with progestogen may lead to increased risk of adverse reactions.[104,105]	1	3 Aripiprazol: concomitant use with progestogen may lead to increased risk of adverse reactions. Pimozida: concomitant use with progestogen may lead to increased risk of adverse reactions.	1	3 Aripiprazol: concomitant use with progestogen may lead to increased risk of adverse reactions. Pimozida: concomitant use with progestogen may lead to increased risk of adverse reactions.	1	1

Category 1: can be administered preferentially without inconvenience. Category 2: coadministration is considered acceptable. Category 3: an alternative treatment or review of the indication of HT is recommended, and its use may be justified in some case. Category 4: coadministration should not be used without justification.
ET, estrogen therapy; HC, hormonal contraception; MHT, menopausal hormonal therapy.

itself or the effects of some of its treatments, which can severely affect their quality of life.

The importance of creating eligibility criteria for pharmacological interactions with HT is that there is some confusion about the suitability of HT in women with morbidities and their treatments, particularly in relation to safety concerns such as an increase in adverse effects, undesirable consequences, or decreased effect of drug that women are taking for their morbility.

The main strength of this project is that it is the first time that categories of eligibility and recommendation (eligibility criteria), based on the best available evidence, are distinguished for the use of HT in these patients with other drugs, using the most rigorous methodological tools. This will provide women's health professionals with a decision-making tool that can be used for the management of menopausal symptoms in women with comorbidities who take medications for it.

This review identifies some important areas of improvement for future research. Few high-quality studies aimed at targeting our objective have been found; in other cases, the interpretations come from basic studies or from extrapolation of HC that uses different preparations and doses.

We expect that our findings will contribute to the development of studies that analyze the safety and efficacy of HT when treating menopausal symptoms in women who take other drugs; however, in any case, here we provide guidance useful for the decision-making process on this topic.

CONCLUSIONS

The available evidence of HT interactions with other drugs comes mainly from biological plausibility, from the knowledge of extensive concomitant use without reported incidents, and from extrapolation of HC. These eligibility criteria can help in the decision process of HT coadministration with another group of drugs. The eligibility criteria should be used based on individualized risk/benefit evaluation and recommendation, according to the underlying pathology, the patient's clinical condition, and the existence or nonexistence of alternatives.

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