TITLE: PHARMACOLOGICAL INTERACTIONS AND MENOPAUSAL HORMONE THERAPY: 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 drugs interactions with HT does not exist, although many midlife women take medications for other conditions. So, 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 each other treatment 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 co-administration: 1: can be used without expected risks; 2: acceptable use (no evidence of negative interaction); 3: Alternative treatment should be considered; and 4: non-use 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 counselling 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 (HC), but there are pharmacological groups in all categories, showing that information is useful. These eligibility criteria summarizes it and can help in the decision process of HT co-administration 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 not of alternatives.

Key words: menopausal hormone therapy, pharmacological interactions, medical eligibility criteria, co-administration drugs, biological plausibility.

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INTRODUCTION

Menopausal hormone therapy (HT) could be used to improve health-related quality of life (HRQoL) in peri 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 contraceptives (HC) prescription, the WHO Medical Eligibility Criteria classifies 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 peri and postmenopausal women concomitantly with different types of treatments for 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 which are 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), 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) peri and postmenopausal women receiving HT; (Intervention) any HT preparation (oestrogens alone or combined with a progestogen, tibolone or tissue selective oestrogen complex) or any route of administration (oral, transdermal, vaginal or intra-nasal); (Outcome) increase/decrease HT effect or drug effect; (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 showed 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 co-administration.

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

Category 1: Co-administration 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 nor biological plausibility suggesting risk.

Category 2: High quality published evidence was not found but co-administration 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 co-administration 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: Co-administration 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 "HT elegibility 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 ~~its~~ composition, dose, and route of administration of HT. Actually, few quality studies aimed to our objective have been found and few provide useful evidence. So, interpretations come from basic studies or from extrapolation of the effects of hormonal contraception (HC). However, for many drugs there is 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: estro-progestogen oral and transdermal), ET (oestrogens only, oral and transdermal), tissue selective oestrogen complex (TSEC) and tibolone, to create a useful table to guide the prescription, and 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 co-administration with other treatments are:

In HT, many different preparations (synthetic and/or natural) with different composition, route of administration and dose are used, and all that implies 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 was done when deemed appropriate and/or there is evidence for that. And in some therapeutic groups, the eligibility assignment may include more than one category because differences within the group that 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. But there are 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 SERMs group, tissue-selective oestrogen complex (TSEC) itself constitutes the only acceptable co-administration with high quality evidence (ECE with bazedoxifeno) . Evidence on possible interactions of SERMs ~~TSEC~~ with the rest of the evaluated drugs was not identified.

However tibolone, although due to its chemical composition would be included among progestogens, has an own column due to its characteristics clinical effects that are comparable to EPT, and because it has some 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 area after two 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 co-administration 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, due to the disease 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 side-effects, undesirable consequences or decrease effect of drug that women is taking for their morbility. The main strength of this project is that is the first time that categories of elegibility 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 comorbilities who take medications for it.

This review identifies some important areas of improvement for future research. Few high quality studies aimed to this target have been found; in other cases, the interpretations come from basic studies or from extrapolation of -HC which uses different preparations and doses. We expect that our findings will contribute to the development of studies to analyse the safety and efficacy of HT when treating menopausal symptoms in women who take other drugs. But, in any case, here we provide a 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 ~~hormonal contraception~~. These eligibility criteria can help in the decision process of HT co-administration with another group of drugs. The elegibility criteria should be used based on an individualized risk/benefit evaluation and recommendation, according to the underlying pathology, the patient's clinical condition, and the existence or not of alternatives.

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TABLE 1: Pharmacological interactions with commonly used drugs and menopausal hormonal therapy

Table 2: Other pharmacological interactions with menopausal hormonal therapy (1)

Table 3: Other pharmacological interactions with menopausal hormonal therapy (2).