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Drug interactions between hormonal contraceptives and psychotropic drugs: a systematic review☆☆,,★

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Abstract

Objective: To examine whether the co-administration of hormonal contraceptives (HC) and psychotropic drugs commonly used to treat anxiety and/or depression results in safety or efficacy concerns for either drug.

Methods: We searched PubMed and Cochrane libraries for clinical or pharmacokinetic (PK) studies that examined co-administration of any HC with psychotropic drugs [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), oral benzodiazepines, bupropion, mirtazapine, trazadone, buspirone, hydroxyzine, monoamine oxidase inhibitors (MAOIs), or atypical antipsychotics] in reproductive aged women.

Results: Of 555 articles identified, 22 articles (18 studies) met inclusion criteria. We identified 5 studies on SSRIs, four on TCAs, one on bupropion, three on atypical antipsychotics and five on oral benzodiazepines. No articles met inclusion criteria for SNRIs, mirtazapine, trazadone, buspirone, hydroxyzine or MAOIs. Overall, clinical studies did not demonstrate differences in unintended pregnancy rates when HCs were administered with and without psychotropic drugs or in psychotropic drug treatment outcomes when psychotropic drugs were administered with and without HCs. PK studies did not demonstrate changes in drug exposure related to contraceptive safety, contraceptive effectiveness or psychotropic drug effectiveness for most classes of psychotropic drugs. However, limited PK data raise concern for HCs increasing systemic exposure of amitriptyline and imipramine (both TCAs), theoretically posing safety concerns.

Conclusion: Limited quality and quantity evidence on use of psychotropic drugs and HCs suggests low concern for clinically significant interactions, though no data exist specifically for non-oral formulations of HC. Given the high frequency of use for both HCs and psychotropic drugs among reproductive-age women in the US, this review highlights a need for further research in this area.

☆☆Conflicts of interest: none.

★Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention nor the Food and Drug Administration.

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Keywords

Hormonal contraception; Drug interactions; Psychotropic drugs; Depression; Anxiety

1. Introduction

Depression is a leading cause of global disability and disease burden. An estimated 8–16% of United States (US) reproductive aged women are diagnosed with depression, 40–50% of whom are receiving prescription pharmacotherapy [1,2]. Concurrent or isolated anxiety is the most common mental health disorder in the US with a lifetime incidence of nearly 29% and is often treated with similar medications used for depression [1,3–5]. Women are 60% more likely than men to experience an anxiety disorder [5].

Multiple studies have demonstrated that depression and anxiety in women of reproductive age are associated with inconsistent, incorrect, or non-use of contraception [6,7]. Studies have also demonstrated an increased risk for unintended pregnancy [8], induced abortion [9], and poor obstetric outcomes in women with depression and anxiety disorders compared with women without these disorders [10–12].

Patients and providers may be concerned about the co-administration of hormonal contraceptives (HCs) with psychotropic medications given the complex pharmacology of these drugs. In general, the estrogen and progestin components in HCs are metabolized by intestinal and hepatic oxidation, glucuronidation and sulfation. Cytochrome P450 (CYP) 3 A4 appears to be one of the major enzymes responsible for the oxidative metabolism of ethinyl estradiol (EE), with other enzymes, namely CYP 2C9, also playing a role. While CYP 3 A4 is also likely involved with the metabolism of progestins, the metabolic pathways for progestins found in HC are incompletely understood. Individual progestins may have different metabolic pathways and thus varied potential for drug interactions. In addition to being metabolized by CYP enzymes, combined oral contraceptives (COCs) are generally considered moderate inhibitors of CYP 1 A2 and weak inhibitors of CYP 3 A4, CYP 2C19 and CYP 2D6 enzymes, leading to additional theoretical concerns for drug interactions [13].

The metabolism of psychotropic agents varies by specific drug. Though some psychotropic agents are inhibitors of CYP enzymes, only one drug, fluvoxamine, is a known inhibitor of CYP 3 A4 and 2C9. The potential for psychotropic agents to *induce* the CYP enzymes, thus theoretically decreasing steroid hormone concentrations, is unknown.

This systematic review aims to identify clinical and pharmacokinetic (PK) data evaluating drug interactions between HCs (including combined or progestin-only oral or non-oral formulations) and psychotropic agents commonly used in the US for the treatment of depression or anxiety. Specifically, we sought studies addressing two research questions: First, among women taking psychotropic medications, does use of HC decrease effectiveness of the psychotropic medication or increase risk for adverse events related to the medication compared with non-use of HC? Second, among women using HC, does use of psychotropic medications decrease contraceptive effectiveness or increase risk for

adverse events related to the contraceptive method compared with non-use of psychotropic medications?

2. Methods

We conducted a systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14].

2.1. Search strategy

We searched PubMed and Cochrane libraries for all articles in any language from database inception to January 13, 2016, using search terms developed with a reference librarian (Appendix A). Reference sections of identified articles were reviewed to help identify additional studies.

2.2. Study selection

We included all published clinical and PK studies in any language. Abstracts, conference presentations, dissertations, and other non-published results were excluded for the formal review. Articles were included if they studied women of reproductive age using any method of hormonal contraception [COCs, transdermal patches, or vaginal rings; progestin-only pills (POPs), injectables, implants; emergency contraceptive pills, or levonorgestrel (LNG) intrauterine devices (IUDs)] in combination with any included psychotropic medication. We used the term oral contraceptive (OC) if a study did not specify whether women were using COCs or POPs or both. We used the term hormonal contraceptive (HC) if a study did not specify route or type of HC administration. Psychotropic medications of interest, identified by consultation with women's mental health experts and review of the American Psychiatric Association's treatment guidelines, were selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), oral benzodiazepines, bupropion, mirtazapine, trazadone, buspirone, hydroxyzine, monoamine oxidase inhibitors (MAOIs), and atypical antipsychotics [3,4]. Clinical outcomes of interest included psychotropic drug effectiveness (e.g. treatment response using depression/anxiety scale scores), contraceptive effectiveness (unintended pregnancy rates, as well as proxy measures including breakthrough bleeding and measures of ovulation) and adverse health effects related to the psychotropic medication or contraceptive method. Studies with PK outcomes of either the psychotropic drug or contraceptive steroid hormone were included.

One author (E.B.B.) performed the database search and screened all titles and abstracts. Two authors (E.B.B. and K.C.) reviewed the full text of all possible articles to determine which articles met inclusion criteria.

2.3. Evaluating the clinical significance of PK parameters

One common method for evaluating possible clinical significance of statistically significant differences in PK parameters is to calculate geometric mean ratios for PK parameters [e.g. geometric mean ratio for area under the curve$_{\text{drug A}}$ (AUC) = AUC$_{\text{drug A}}$ in users of drug B/AUC$_{\text{drug A}}$ in non-users of drug B ×100], construct 90% confidence intervals (CIs) around that ratio and set a pre-defined range (typically a 90% CI of 80–125%) that would suggest a

lack of interaction [13]. Studies were not required to perform these calculations for inclusion in this review; however, if performed these calculations were used to interpret clinical significance.

2.4. Study quality assessment

Study design, sample size, validity, and generalizability were used to assess study quality. All clinical studies were assigned quality using the three-level United States Preventative Services Task Force grading scale (good, fair, poor) [15]. As no standard guidelines exist to assess quality of PK studies, we designed a 7-item quality rating system and applied it to the identified PK articles (Appendix B). The quality of each study was assigned independently by two authors. Any differences were resolved through discussion with a third author.

2.5. Data synthesis

The data were assessed and summarized using standard abstraction forms. We constructed separate evidence tables for each class of psychotropic drug. Meta-analysis could not be conducted due to heterogeneity of study design and outcomes, as well as limited data in most classes of drugs.

3. Results

We identified 555 articles, of which 18 studies described in 22 articles met inclusion criteria. Five studies reported on SSRIs [16–21], four on TCAs [22–25], one on bupropion [26], three on atypical antipsychotics [27–29] and five on oral benzodiazepines [30–35]. No studies of women using SNRIs, mirtazapine, trazadone, buspirone, hydroxyzine, or MAOIs were identified that met inclusion criteria.

3.1. SSRIs (Table 1)

3.1.1. Clinical outcomes — SSRIs—A secondary analysis of the United States Fluoxetine Clinical Trials database included 17 randomized placebo-controlled trials of fluoxetine [16]. Women used a wide range of fluoxetine doses (5–80 mg) with follow-up ranging from 5–16 weeks. A woman was classified as an OC user if she had used an OC (any formulation) at any time during the blinded treatment period. In addition, 4.5% of OC users were taking medroxyprogesterone (route of administration not specified), which is not generally considered an oral contraceptive, raising concern for misclassification of these women. Contraceptive use for the non-OC group was not reported. The analysis compared OC users and non-users within each trial arm (fluoxetine and placebo), and across treatment arms (e.g., OC users in the fluoxetine arm vs OC users in the placebo arm). There was no statistically significant difference between fluoxetine + OC users and fluoxetine alone users in fluoxetine treatment response (pN.15) as measured by changes in three depression or anxiety scales [Hamilton rating scale for depression (HRSD), HRSD anxiety/somatization subscale and HRSD retardation subscale]. In addition, no statistically significant difference was seen in the unintended pregnancy rate for OC + fluoxetine users (2/232; 0.9%) compared with OC + placebo users (0/121; 0%) (p=.11). Among women using fluoxetine, rates of treatment-emergent adverse events were similar between OC users and non-users. However, women taking OCs with fluoxetine had a small increased odds of

headache (odds ratio [OR] 2.1; 95% CI 1.2–3.6) compared with OC + placebo users. For non-OC users, the odds of experiencing a headache were not statistically different between fluoxetine and non-fluoxetine users (Table 1) [16].

One prospective cohort examined treatment response after 12–14 weeks of citalopram among women with major depressive disorder ($HRSD_{17}$≥14) [17]. The primary outcome was odds of remission ($HRSD_{17}$≤7) in women using HC (n=226) versus those not using HC (n=670). Doses and formulations of HC were not reported and contraceptive use among the non-HC group was not described. No significant difference was seen in the adjusted odds of remission for HC users compared with non-HC users. No significant differences were seen in side effects between HC users and non-HC users (all PN.05) [17].

3.1.2. Pharmacokinetic outcomes-SSRIs—A PK study of citalopram included 16 adolescents (age 16–20) using citalopram (10–60 mg) with a diagnosis of major depressive disorder or dysthymia. Ten participants were taking COCs, but duration of use and formulation varied. Standard PK measures (e.g. AUC or C_{max}) were not reported. A significant concentration/dose correlation was found for citalopram and its metabolite, demethylcitalopram (DCIT), for non-COC users [citalopram r^2 0.75 (p=.02); DCIT r^2 0.71 (p=.03)] but not for COC users [18,20]. The clinical interpretation of this finding is unknown.

A post-marketing surveillance study compared 11 “hormone-based contraceptive” users with 42 age-matched non-users all taking escitalopram (S-CIT) [19]. For the total study population (n=155), the mean daily dose of escitalopram was 20 mg (5–40 g); however, details about the citalopram dose for the contraceptive study population were not given. Women in the HC group had a significantly lower S-DCIT/S-CIT ratio than non-users (0.46 vs. 0.74; p=.02). All other dose-normalized concentrations or ratio differences were not significant (data not shown) [19]. Again, the clinical interpretation of this parameter is not known.

Only one study investigated the effects of SSRIs (vortioxetine) on the contraceptive [21]. In a single-blind, randomized, crossover study, 28 healthy women (age 18–45) were administered a COC [ethinyl estradiol (EE)/LNG 30/150 mcg] plus placebo for 21 days followed by the same COC (EE/LNG 30/150 mcg) plus vortioxetine 10 mg orally for 21 days. The C_{max} ratios for both hormones showed small but statistically significant differences with vortioxetine; EE decreased 6.1% and LNG increased 7.1% [21]. However, none of 90% CIs exceeded the no-effect boundary of 80–125%. The geometric mean AUC ratios for EE and LNG between placebo and vortioxetine were not significantly different.

3.2. TCAs (Table 2)

3.2.1. Clinical outcomes — TCAs—One retrospective cohort study examined 114 reproductive aged women with depression taking clomipramine, and evaluated treatment response and clomipramine-related adverse events for women taking OCs or not [36]. The drop-out rate due to adverse events was equal in both groups. In a nested case–control analysis, investigators compared the 18 OC users with 18 matched non-OC users and found

no difference in the depression response to clomipramine (not objectively defined) or the pattern of adverse events [36].

A study examining clomipramine with COCs was reported in four articles [22–25]. Women with depression (n=46) were treated with clomipramine. Although baseline depression rating scale scores were higher in the COC users than in non-users, significant improvements (decreased scores) occurred in both groups at 2 and 4 weeks (p values not given) [22]. While COC users also had greater sleep disturbances and loss of libido than non-users at baseline, at the end of the study there were no differences in treatment related adverse events (p values not given) [22] or study dropout due to side effects (p value not given) [23]. Mean plasma clomipramine concentrations did not significantly differ across the 4-week study period (p values not reported) [23,25]. No significant correlations were seen between depression rating scores and clomipramine plasma concentrations for either COC users or non-users [24].

3.2.2. Pharmacokinetic outcomes — TCAs—

One study evaluated the PK of imipramine among COC users and non-users [38]. Eleven healthy women aged 20–39 (six COC users and five non-users) were given a single 50 mg dose of imipramine. The AUC of imipramine was 104.4% greater for COC users than non-users (415 vs 203 ng/mL·per hour (p<.05). The $t_{1/2}$ of imipramine did not differ between groups [38].

As a subset of a larger efficacy trial, one study reported serum concentrations of amitriptyline (AT) for five OC users and 13 non-OC users taking oral AT 25 mg daily for 6 weeks [37]. Day 36 mean serum concentration of AT was 89.7% higher in OC users compared with non-OC users (74 vs. 39 mcg/L, p=.0007) and the mean serum concentration of the metabolite (Z-10-OH-NT) was 100% higher (14 vs. 7 mcg/L, p=.02). Concentrations at other time points or other standard PK measures were not reported [37].

3.3. Bupropion (Table 3)

In a single PK study of women using bupropion and HCs, 12 healthy women (age 20–25) were administered a single dose of bupropion (150 mg) in phase 1 [26]. In phase 2, the women were pretreated with a COC (30 mcg EE and 150 mcg desogestrel) for 10 days and on day 10 administered a single dose of bupropion (150 mg). The $AUC_{bupropion}$ for the COC phase was 19% less than with bupropion alone (0.72 vs. 0.89 mcg/mL·per hour; pb.001). For the active metabolite, the $AUC_{hydroxybupropion}$ for the COC phase was 31% less than with bupropion alone (11 vs. 16 mcg/mL·per hour; pb.001), and the C_{max} was also significantly less with COCs compared to bupropion alone (20% decrease; p=.009). The ratio between the AUC of the active metabolite to bupropion was not significantly different between phases [26].

3.4. Atypical antipsychotics (Table 3)

In a double-blind placebo controlled cross-over trial, 19 healthy women were administered a COC (30 mcg EE and 150 mcg LNG) for 21 days plus a placebo or ziprasidone (40 mg/day in divided doses) on days 8–15. [27] No difference in the AUC or C_{max} for either steroid hormone was seen in the placebo compared with ziprasidone arms. This study also collected limited information on treatment-related adverse events. There were no serious adverse

events and most mild–moderate adverse events were typical of those seen on ziprasidone therapy alone; however, the study did not include women using ziprasidone alone [27].

Data from a routine therapeutic drug monitoring center in Norway were examined to investigate potential interactions between HCs and olanzapine [28]. Dose-adjusted olanzapine concentrations (and metabolites) were compared for reproductive aged women on estrogen-containing contraceptives (n=10), progestin-only contraceptives (n=10) or non-contraceptive users (n=129). A 33% decrease in the dose adjusted concentration of the metabolite (N-desmethyl olanzapine) was seen for estrogen containing contraceptive users compared with non-contraceptive users (1.3 vs 1.95; p=.03). No other significant differences were seen in the dose-adjusted olanzapine or metabolite concentrations among groups [28].

In a double-blind placebo controlled cross-over trial, 17 healthy women (age 18–40) were administered a COC (35 mcg EE and 180–250 mcg norgestimate) daily for 28 days plus a placebo or lurasidone (40 mg) on days 12–21 [29]. The AUC and C_{max} values of both steroid hormones on day 21 were similar between placebo and lurasidone treatment arms. In addition, the 90% CIs for the geometric mean ratios did not exceed the no-effect boundary. One subject experienced dysmenorrhea while taking COC plus lurasidone but no serious treatment-related adverse events were reported [29].

3.5. Oral benzodiazepines (Table 4)

In a non-randomized, non-blinded trial, women (age 19–37) using COCs (50 mcg of EE or less, n=17) and controls not taking COCs (n=14), matched to COC users by smoking status, were administered a single dose of oxazepam (30 mg) [30]. No significant differences were observed in volume of distribution (Vd), elimination half life, total clearance or free fraction of oxazepam in plasma between users and non-users of COCs. AUC, t_{max} and C_{max} were not reported.

A smaller non-randomized, non-blinded trial examined PK parameters for a single dose of oxazepam (45 mg) in healthy women (age 21–33) taking a 50 mcg EE COC for at least 6 months (n=5) and controls not using COCs (n=6) [32]. No changes to oxazepam Vd was observed, though clearance increased by 157% (pb.01), and a nonsignificant decrease in elimination half life was reported. AUC, t_{max} and C_{max} were not reported.

Two non-randomized, non-blinded parallel studies examined four benzodiazepines administered with COCs [31,35]. Women taking COCs with 35 mcg of EE or less (n=19) and matched controls not taking COCs (n=21) received single doses of either (study 1) temazepam (30 mg) and triazolam (0.5 mg) or (study 2) alprazolam (1 mg) and lorazepam (2 mg) in two sequential COC cycles. In a parallel analysis, they observed no significant difference in any PK parameter between COC and non-COC users during administration of triazolam. However, COC users taking alprazolam demonstrated a higher AUC and lower elimination rate constant than non-users, with no changes to other parameters. COC users taking lorazepam had higher elimination rate constant, while COC users taking temazepam demonstrated a higher elimination rate constant and lower AUC than non-COC users taking either drug. Other parameters were unchanged. For clinical outcomes, COC users experienced greater impairment of psychomotor performance than non-users after taking

alprazolam, lorazepam, and triazolam [31]. This increase in psychomotor impairment did not correlate with PK changes. COC users did not differ from non-users in measures of sedation and memory for any of the four benzodiazepines, though the study was underpowered for these outcomes.

One non-randomized, non-blinded study examined PK parameters after a single alprazolam (1 mg) dose in COC users (less than 50 mcg EE, n=16) and non-users (n=23) [33]. AUC, half life, Vd and clearance did not differ between groups; C_{max} and t_{max} were not reported.

One observational study reported the incidence of breakthrough bleeding in 72 women taking COCs (EE ≤50 mcg) in combination with an oral sedative (diazepam 5 mg [n=15], chlordiazepoxide 5 mg [n=19], nitrazepam 5–10 mg [n=21], or meprobamate 200 mg [n=17]) [34]. No woman experienced breakthrough bleeding prior to initiation of the sedative, whereas 36.1% of women reported breakthrough bleeding after initiating a sedative, with most breakthrough bleeding occurring in users of chlordiazepoxide and meprobamate (Table 4). Only one of 15 diazepam users and two of 21 nitrazepam users reported breakthrough bleeding. This study did not control for dose or duration of use of the sedatives and no statistics were performed. No pregnancies were observed but the duration of follow up was not reported [34].

4. Discussion

This review identified 18 studies, primarily of fair to poor quality, which examined potential interactions between HCs and medications commonly used to treat anxiety or depression.

4.1. SSRIs

Limited data from five studies of co-administration of SSRIs and HCs overall suggest low concern for clinically significant interactions. One study found no difference in pregnancy rates in OC users taking and not taking fluoxetine [16]. Another found no difference in depression scales for HC versus non-HC users treated with citalopram [17]. However, these studies are of fair quality due to several limitations, such as not specifying how unintended pregnancy was measured, lack of information on response and follow-up rates, being unable to correlate time of unplanned pregnancy with OC use/compliance and not controlling for potential confounders [16,17]. Exposure to HCs (or OCs) was inadequately defined and/or measured and a wide range of types and doses of HCs were likely used.

Two PK studies of SSRIs and HCs were of poor quality due to the uncertain clinical relevance of the PK parameters measured, small sample size for parallel designs and a wide range of doses of both drugs [18–20]. One good quality PK study with the SSRI-like antidepressant vortioxetine was the only study to examine the PK parameters of the contraceptive hormones with use of an SSRI, and it reassuringly showed no clinically significant interactions [21].

4.2. TCAs

Limited data from five studies of co-administration of TCAs and HCs overall suggest limited concern for clinically significant interactions. Two poor quality clinical studies of

TCAs with HCs showed no increase in adverse events from the TCA. However, these studies were limited by the wide type and variety of OCs used, small sample sizes (n=15–20 per group) and high drop-out rates (N20%) (Table 2) [22,36]. The PK evidence for TCAs with OCs is of fair-poor quality but demonstrates no significant PK interaction with clomipramine, and a possible increase in concentrations of amitriptyline and imipramine among OC users compared with non-OC users [37,38]. However, the two PK studies that demonstrated increased concentrations of the TCA with amitriptyline and imipramine were of poor quality and limited by very small sample sizes (5 or 6 OC users per study), inclusion of a wide range of OC doses and formulations, failure to report AUC and C_{max}, and failure to state exposure assessment (Table 2). In addition, one study included only women with bulimia, which may have resulted in highly variable intake and absorption of medications [37]. Thus, although these studies raise concern that co-administration of OCs with certain TCAs might lead to increased exposure to that TCA, and thus theoretically have an increased potential for TCA-related adverse events, the data are fair to poor quality and cannot be clinically applied with full confidence. No studies were identified, either PK or clinical, that evaluated whether TCAs induce or inhibit HCs or affect contraceptive effectiveness.

4.3. Bupropion

One good-quality PK study demonstrated a modest decrease in the exposure to bupropion in COC users compared with non-users. [26] Strengths of the study included using a crossover design, measurement of appropriate PK parameters, and administration of the same COC to each subject. Given the small reduction in exposure to bupropion, theoretical concern for decreased clinical efficacy of bupropion among COC users exists. However, the clinical effect of a reduction of this magnitude is uncertain.

4.4. Atypical antipsychotics

Although no clinical studies were identified, PK data from three fair to good quality studies examining the co-administration of atypical antipsychotics and HCs suggest low concern for significant interactions. Two good quality studies examined steroid hormone PK parameters, and neither demonstrated any significant changes in the AUC or C_{max} for the estrogen or progestin component of COCs [27,29]. Both used a crossover design, a single COC type/dose and measured clinically relevant PK parameters. One fair quality study that examined the PK parameters of olanzapine demonstrated no significant difference in the exposure of olanzapine between progestin-based contraceptive users, estrogen containing contraceptive users or non-contraceptive users [28]. It did demonstrate a decreased concentration of the metabolite N-desmethyl olanzapine in users of estrogen-containing contraceptives compared with the other two groups; however, the clinical relevance of this finding is unknown [28]. Though limited to PK data, the lack of interaction between HCs and atypical antipsychotics is more reassuring than data for other classes of psychotropic drugs due to the higher quality of studies.

4.5. Oral benzodiazepines

Data from four fair quality PK studies showed minimal interaction of COCs on oral benzodiazepines and COCs. Two of these studies are limited by use of PK parameters

of uncertain clinical significance [30,32]. Those which did address AUC and C_{max} of the benzodiazepine did not demonstrate any consistent direction of change for this class of drugs when co-administered with COCs [33,35]. While some benzodiazepines are metabolized by the cytochrome P450 system (alprazolam), others such as lorazepam and oxazepam are not, which could explain the heterogeneity in these results. Given the inconsistent and small magnitude of changes in PK, as well as one study which showed no difference in sedation or memory during co-administration of four benzodiazepines with COCs [31], these fair quality studies suggest minimal concern for a clinically significant interaction between COCs and oral benzodiazepines.

4.6. Theoretical concerns and drug metabolism

As the available published evidence examining drug interactions between HCs and psychotropic drugs used to treat anxiety and depression is limited, it is useful to consider theoretical concerns for possible interactions, i.e. the potential for a psychotropic drug to inhibit or induce the metabolic pathways of HCs and the potential for HCs to inhibit or induce the metabolic pathways of psychotropic drugs. We considered minor inducers or inhibitors as unlikely to cause clinically significant interaction, thus, we looked for at least moderate inhibitors or inducers of relevant CYP P450 enzymes. While several of the psychotropic drugs included in this review are thought to have minor inhibitory effects on the important CYP P450 enzymes in the HC pathway (CYP 3 A4 and CYP 2C9), none of the psychotropic drugs are moderate or strong inhibitors those enzymes [13]. Thus, limited theoretical concern exists for any of the psychotropic drugs to significantly inhibit HCs leading to increased concentrations of steroid hormones and posing contraception-related safety concerns.

Psychotropic drugs may also induce HCs. However, as little is known about the potential for psychotropic agents to induce CYP 450 enzymes, the theoretical concern for psychotropic drugs causing a decrease in steroid hormones concentrations, thus potentially decreasing contraceptive effectiveness, is unknown. This review identified four studies (one clinical and three PK) that addressed this concern and none demonstrated a significant effect of the psychotropic agent on HC concentrations [16,21,27,29]. Thus, limited clinical and PK data do not suggest a concern for decreased contraceptive effectiveness when HCs are co-administered with the psychotropic drugs in this review.

Next, we consider possible effects of HCs on psychotropic drugs. As COCs are considered as a moderate inhibitor of CYP 1 A2, when co-administered with psychotropic drugs metabolized by CYP 1 A2 (duloxetine, clomipramine, imipramine, amitriptyline, olanzapine, clozapine, ziprasidone and mirtazapine), COCs (and perhaps other HCs) may result in increased exposure to the psychotropic agents and potentially pose safety concerns [13]. Fair-to-poor quality studies in this review suggest that clomipramine [22–25] and olanzapine [28] PK are not significantly affected by HCs, but poor quality studies suggested that imipramine and amitriptyline concentrations may be increased by OCs [37,38]. No published articles were identified to address this concern for duloxetine, mirtazapine or clozapine. However, we identified four case reports not meeting criteria for this review that associated COC use with increased systemic exposure of clozapine leading to

clinically significant adverse events such as pericarditis and severe fatigue, weakness and dizziness [39–42]. The finding that some TCAs may have increased concentrations when co-administered with HCs is of concern as many TCAs have narrower therapeutic windows than other psychotropic agents. TCAs are less often used to treat depression and anxiety disorders given the more favorable safety profile of newer agents such as SSRIs; however, they are used to treat chronic pain disorders and chronic migraines, which commonly affect women of reproductive age. In summary, although theoretical concern exists for HCs to moderately inhibit the metabolism of certain psychotropic drugs (metabolized by CYP 1 A2), the scant data which explore this concern are reassuring except in the case of amitriptyline, imipramine and clozapine, an atypical anti-psychotic. Further research examining the safety of these drugs with HC is needed.

There is no known theoretical concern for HCs to induce CYP enzymes, thus HCs are not likely to decrease concentrations of psychotropic drugs and lead to treatment failures. In the four clinical studies in this review that examined this question, no significant differences in psychotropic drug efficacy were found [16,17,22,36]. The only PK study to find a significant decrease in psychotropic drug concentrations examined bupropion with COCs [26]. The proposed mechanism of action for this finding is thought to be from EE potentially inhibiting the enzyme CYP 2B6, which is responsible for hydroxylation of bupropion into its active metabolite. Thus, inhibition of CYP 2B6 decreases conversion of bupropion into the active metabolite, resulting in increased concentrations of bupropion (inactive form) but decreased concentrations of the active drug. No clinical data are available to further investigate this interaction.

One strength of this review was our inclusion of all study designs on a wide range of psychotropic agents. However, this review is limited by the scarcity of published evidence, mostly of fair to poor quality, thus limiting definitive conclusions. Additionally, there is virtually no published information on the use of progestin-only methods or non-oral contraceptives (including long-acting reversible methods) with psychotropic drugs. One study attempted to differentiate between combined hormonal contraceptives and progestin-only contraceptives [28] but all other studies examined OCs only, often not specifying combined or progestin-only oral contraceptives. Due to potential differences in drug metabolism and drug interactions with different types of progestins and routes of administration, the findings of the studies included in this review cannot be assumed to apply to progestin-only or non-oral HC formulations. Likewise, many common drugs (e.g. sertraline, mirtazapine) and even entire classes of psychotropic agents (e.g. SNRIs and MAOIs) did not have any published data examining drug interactions with HCs. Given the high frequency of use for both HCs and psychotropic drugs among reproductive age women in the US, this review highlights a great need for further research in this area [43,44]. Well designed, good quality PK and clinical studies of commonly used psychotropic drugs with oral and non-oral HC could add substantially to the field.

The limited evidence on drug interactions between psychotropic drugs used to treat anxiety and depression and HCs suggests low concern for clinically significant interactions. However, theoretical concern, supported by limited PK studies, indicates that concomitant use of COCs and certain TCAs could have the potential to increase exposure to the

TCA, potentially posing safety concerns for drugs with narrow therapeutic windows. The metabolism of HCs and psychotropic drugs is complex and often uncertain. No data exists on drug interactions for non-oral formulations of HC or for several classes of psychotropic drugs. Given the public health importance of providing guidance on the safety of contraceptive method use to prevent unintended pregnancies among women with depression and anxiety disorders, future clinical and pharmacokinetic studies are needed to investigate the safety and effectiveness of contraceptive use among women taking psychotropic drugs.

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Appendix A

PubMed: (tricyclic antidepressant OR snri OR fluoxetine OR alprazolam OR sertraline OR citalopram OR lorazepam OR trazodone OR escitalopram OR duloxetine OR bupropion OR venlafaxine OR diazepam OR paroxetine OR quetiapine OR risperidone OR aripiprazole OR buspirone OR hydroxyzine OR olanzapine OR desvenla-faxine OR ((“Serotonin Uptake Inhibitors”[Mesh]) OR ssri) OR “Antipsychotic Agents”[Mesh] OR “Anti-Anxiety Agents”[Mesh] OR “Antidepressive Agents” [Mesh] OR psychotropic drugs[Mesh]) or antipsychotic or antipsychotics AND (“Contraceptives, Oral, Combined”[Mesh] OR “Contraceptives, Oral”[Mesh] OR “Contraceptives, Oral, hormonal”[Mesh] OR “Contraceptives, Oral, Combined”[Pharmacological Action]) OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR “ortho evra” OR NuvaRing OR (progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR “Levonorgestrel”[Mesh] OR Levonorgestrel OR “Norgestrel”[Mesh] OR norgestrel OR etonogestrel AND contracept*) OR dmpa OR “depot medroxyprogesterone” OR “depo provera” OR “net en” OR “norethisterone enanthate” OR “norethindrone enanthate” OR (contracept* AND (inject* OR implant)) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR (levonorgestrel-releasing two-rod implant) OR “Intrauterine Devices”[Mesh] OR “Intrauterine Devices, Copper”[Mesh] OR “Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR IUCD OR IUS OR mirena OR Skyla OR paragard OR “Copper T380” OR CuT380 OR “Copper T380a” OR “Cu T380a”) NOT (“Animals”[Mesh] NOT “Humans”[Mesh]).

Cochrane: Contraception AND Depression; Contraception AND Psychotropic

Appendix B. Quality rating system for pharmacokinetic studies

Three Overall Quality Categories:

Good: No important limitations. Well done study that meets all criteria for an adequate pharmacokinetic (PK) study (below). Reviewer feels confident the results are internally valid.

Fair: Clear limitations to study design but no fatal flaws.

Poor: One or more fatal flaws that likely invalidates results.

Criteria	Good (meet all criteria)	Fair	Poor (has one or more)
Design	Crossover design (or parallel design with appropriate justification)	Parallel design	
Sample Size	Cross-over n≥12; if parallel design, *n* should be higher	*n* is 8–12	*n*<8
Exposure	Clear definition of exposure (clearly defined drug(s), dosages, and frequency). Clearly stated exposure assessment accounting for ensured exposure to drug (in d-d-I studies, exposure to both drugs clearly defined).	Clear definition of exposure. Adequate but less than ideal exposure assessment (self-report alone).	Exposure not defined. No exposure assessment.
Outcome	Appropriate PK parameter mea sured for desired outcome (e.g., for hormonal contraception *C*max, AUC or C_{avg}.; for non-oral formulation $C_{average}$ or AUC) and the measured out come has clinically meaningful relevance (known or theoretical).	PK parameter less than ideal but still give some potentially useful information.	Clinically irrelevant PK parameter.
Timing	Time of the blood draw(s)/ testing appropriate for the desired outcome. Repeated measures taken (unless steady state demonstrated to be achieved, then one-time measurement OK).	Time of blood draw not ideal but still yields useful information. One-time measurements.	Time of blood draw out of range to yield meaningful information in relation to desired outcome.
Intersubjective variability	Methods minimize possibility for intersubjective variability. (e.g., range of timing for blood draws). There is adequate control in studies for factors known to impact metabolism (age, BMI, other medications, or other known risk factors) as appropriate/needed.	Moderate intersubjective variability. Some controlling for factors known to impact metabolism or no theoretical factors known to impact so no controlling done.	Very large intersubjective variability. No control and clear presence of factors that very likely impacted metabolism between subjects.
Population	Appropriate population chosen (e.g., reproductive-aged women).	Less than ideal population but not fatally so.	Completely wrong population chosen that has proven or likely will have different metabolism/effect of the drugs.
Steady state of perpetrator drug (Victim drug OK for one-time dose)	Clearly allowed for perpetrator drug to be in steady state at time of evaluation.	Likely that perpetrator drug was in steady state; however,methods not clearly defined or uncertain of SS actually reached.	Perpetrator drug clearly NOT in steady state.
Assay/analyses and validation	Study described methods for analysis and validation of analyses.	Study did not describe methods for analysis and validation of analyses.	Methods described for analysis or validation described but methods used known to be

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Table 1

Evidence table for use of selective serotonin reuptake inhibitors (SSRIs) with hormonal contraception

Author, year, funding source	Design	Study population	Exposure psychotropic drug	Exposure contraceptive	Outcomes	Results	Strengths	Limitations	Quality
Clinical Studies for SSRIs									
Koke, S. 2002 Eli Lilly and Company	Retrospective cohort; secondary analysis of 17 RCTs	1698 females, ages 15–45, with major depression, OCD, or bulimia *353 OC users (232 fluoxetine/121 placebo)* *1345 non-OC users (913 fluoxetine/432 placebo)*	Fluoxetine (5–80 mg) vs. placebo	OCs vs non-OCs, otherwise undefined, used at any point during the study period (range 5–16 weeks)	HRDS-17 scores for changes in depression symptoms Unplanned pregnancy Treatment-emergent adverse events (occurred for first time or worsened during treatment period)	No statistical interaction between fluoxetine and OCs on changes in depression scores over the study period (p>.15 for all measures) Unintended pregnancy: Fluoxetine +OC: 2/232 Placebo +OC: 0/121 (p=.11) Adverse events equal except headache (p=.042), asthenia (p=.021), and pain (p=.031) greater in Fluoxetine group Increased headaches in OC users (OR 2.1,1.2–3.6) Fluoxetine was superior to placebo in all measures for improvement of depression equal among OC vs non-OC users	Large sample size Only study to look at unplanned pregnancy outcomes	Varied dosages of SSRI No information on follow-up rates across studies OC use may not have occurred at the time of unintended pregnancy; unclear how OC use was measured, unclear who was in the comparison group (may have included other hormonal contraceptive methods), range of doses and formulations No information on how unplanned pregnancy was measured No control for potential confounders other than study	II-2, Fair
Kornstein, S. G. 2013 National Institute of Mental Health grant and medications provided by Bristol-Myers Squibb, Forest Laboratories,GlaxoSmithKline, King Pharmaceuticals, Organon, Pfizer, and Wyeth	Prospective cohort	Premenopausal women with Major Depressive Disorder, (HRSD-17>14) age<40 given citalopram for up to 14 weeks	Citalopram dose titrated to effect	Hormonal contraceptives (all types)	-Depression scales-HRSD17, QIDS-SR16 and the QIDS-C16 over 14 weeks -Frequency, Intensity, and	HC vs no HC, adjusted OR, 95% CI HRSD17: 1.2, 0.9–1.8 QIDS-SR remission:1.2, 0.9–1.9 QIDS-SR response:1.2, 0.8–1.6 No difference in side effect frequency	Adjusted for baseline demographic and clinical features that differed between groups at baseline	No information on response rates or follow-up rates use was measured, unclear who was in the	II-2, fair

Author, year, funding source	Design	Study population	Exposure psychotropic drug	Exposure contraceptive	Outcomes	Results	Strengths	Limitations	Quality
		(*n*=896) *226 HC users* *670 non-HC users*			Burden of Side Effects Rating Scale-Adverse events	(p=.62), intensity(p=.68) or burden (p=.21) and no difference in exiting the study (14.2% vs 17.8%; p=.21) or serious adverse events (3.5% vs. 3.6%; p=.98)		comparison group (may have included other hormonal contraceptive methods), range of doses and formulations.	
PK studies for SSRIs									
Carlsson. 2001 and Reis, 2002 H. Lundbeck, the Lion research fund, and Swedish Medical Research Council	PK Parallel	Adolescents females with major depressive disorder or dysthymia on citalopram (*n*=16) *10 COC users* *6 non-OC users*	Citalopram (10–60 mg) for>2 months	COCs (any type)	Steady state plasm concentration of the S and R enantiomers of citalopram and metabolites (DCIT and DDCIT) Concentration/ dose ratio correlations for citalopram and metabolites Single trough value (10–30 h)	Sig. correlation of S/R ratio for citalopram/ DCIT in women not taking COCs (r=0.963, pb.001) however no sig correlation in those taking COCs (r=0.403, p=.24) Concentration/dose correlations:citalopram: r^2 0.33 (p=.08) COC users vs r^2 0.75 (p=.02) DCIT: r^2 0.33 (p=.08) COC users vs r^2 0.71 (p=.03) DDCIT: r^2 0.33 (p=.15) COC users vs r^2 0.23 (p=.41)		Unclear clinical relevance of primary outcomes Wide range of timing for blood samples (10–30 h after last dose) Wide range of citalopram dose Unclear how COC use was measured, unclear who was in the comparison group (may have included other hormonal contraceptive methods), range of doses and formulations	poor
Reis, M. 2007 H Lundbeck AB, Berzelius Clinical Research Center	PK Parallel	Women taking escitalopram for various diagnoses on HC (*n*=11) vs age matched women not on any hormones (*n*=42)	Escitalopram (5–40 mg)	Hormonal contraceptives (all types)	S-DCIT/ Scitalopram ratio Adverse events Two trough values (10–30 h)	S-DCIT/S-citalopram ratio HC users vs non-users 0.46 vs 0.75 (p=.02) Authors concluded clinical impact likely low.	Age matched controls	Unclear clinical relevance of primary outcome Wide range of citalopram dose (5–40 mg) Wide range of timing for blood samples (10–30 h after last dose)	poor

Author, year, funding source	Design	Study population	Exposure psychotropic drug	Exposure contraceptive	Outcomes	Results	Strengths	Limitations	Quality
								however when corrected for time then no differences seen.	
Chen, G. 2013. Takeda Pharmaceutical company and H. Lunbeck A/S	PK Single-blind, randomized, placebocontrolled, 2-sequence, 2-period, crossover	Healthy non pregnant women 18–45 years, BMI 18–30 kg/m^2(n=28)	Placebo + COC for 21 days, Crossover 35 day washout Vortioxetine 10 mg + COC for 21 days, crossover	EE/LNG 30/150 mcg	AUC_{24}, C_{max} of EE/LNG (ratio of parameters vortioxetine/ placebo)	EE: AUC ratio no change (test/ reference) 99.1 (96.2–102.3) LNG: AUC ratio(test/ reference) 93.9 (89.3–106.75) EE: Cmax ratio ↓ 6.1% (test/reference) 93.9 (89.3–98.7) LNG: Cmax ratio ↑ 7.1% (test/reference) 107.1 (100.9–113.65)	Crossover design, adequate sample size, single COC used, meaningful outcome	Rare antidepressant used Not a traditional SSRI; works via serotonin reuptake inhibition and receptor activity. Healthy women, not women with depression	good

C_{max}, Maximum concentration; OCD, obsessive–compulsive disorder; OR, odds ratio; QIDR-C16, quick inventory of depressive symptomatology–clinician rated; QIDS-SR16, quick inventory of depressive symptomatology–self-report; RCT, randomized control trial.

Table 2

Evidence table for use of tricyclic antidepressants (TCAs) with hormonal contraception

Author, year, funding source	Design	Study population	Exposure psychotropic drug	Exposure contraceptive	Outcomes	Results	Strengths	Limitations	Quality
Clinical studies for TCAs									
Beaumont, G. 1973 Funding source not stated	Retrospective cohort with nested case control	114 female patients with depression taking clomipramine *30 OC users/18 completed* *84 non-OC users/18 matched non-OC users completed*	Clomipramine	OCs	Response of depression to clomipramine (not otherwise defined)	No difference in drop-out rate due to side effects (22 vs. 23%) No difference in treatment response No qualitative difference in type of side effects	Non-OC users matched by age, clomipramine dose, previous treatment, type of depression and physician	Multiple OC formulations/doses used Dose(s) of clomipramine not stated Unclear how outcomes defined or measured, no statistics reported High dropout rate (22–23% in each group) Follow-up time not reported	II-2, poor
Gringras, M. 1980. Funding source not stated (PK outcomes reported in John, Seldrup and Luscombe)	Prospective cohort	Women with depression age 18–40 suitable for treatment with clomipramine *21 COC users/15 completed* *25 non-OC users/20 completed*	Clomipramine 25 mg orally at bedtime for 4 weeks	COC use (any type with either 0.015 or 0.03 mg EE) for>2 months	GPCR depression rating scale at 0,2,4 weeks	GPCR depression scores, at baseline➔4 weeks COC users-28.1➔ 10.9 Non-OC users-22.4 ➔ 8.5 No difference in side effects. No statistics performed		Unclear how COC use was measured with a mix of doses and formulations used Groups not similar at onset with regard to initial severity of depression. Unclear if statistics performed on differences in individual side effects.	II-2, poor
PK studies for TCAs									
a) John, vs. A. 1980 b) Luscombe, 1980 c) Seldrup, 1980 Funding source not stated (See Gringas, 1980 for clinical outcomes)	PK Parallel	Women aged 18–40 with depression, *n*=46 a) *21 COC users/15 completed* *25 non-OC users/20 completed* b) *19 COC users/14 completed* *23 non-OC users/20 completed* c) *11 COC users* *16 Non-OC users*	Clomipramine 25 mg orally at bedtime for 4 weeks	COC use (any type with either 0.015 or 0.03 mg EE) for >2 months	a) Mean plasma clomipramine across 4 weeks and dropout rate for side effects b) Mean plasma clomipramine at 4 weeks c) Correlation between clinical response and steady state plasma levels of clomipramine	All results reported as “not significant but no p-values given a) Side effects: 13% COC users vs. 10% non-OC users Mean plasma level across 4 weeks COC users 14 ng/ml vs non-OC 17 ng/ml b) Mean plasma levels (day 28) COC users 13.2 ng/ml vs. non-OC 16.8 ng/ml c) OC users-r=0.1 Nonusers- r=−0.42	Steady sate of perpetrator drug achieved, repeated blood sampling over 4 weeks	Unclear how COC use was measured with a mix of doses and formulations used Results didn’t report on depression scale findings just stated “Clinical response and tolerability in the two groups were also similar” Limited relevance of PK parameters since only concentrations given	Fair

Author, year, funding source	Design	Study population	Exposure psychotropic drug	Exposure contraceptive	Outcomes	Results	Strengths	Limitations	Quality
Abernethy, D. R. 1984 U.S. Public Health Service and Charles A, King Trust, Inc.	PK Parallel	Healthy women age 20–39, within 20% of ideal body weight on COC for >3 months *6 COC users* *5 nomedication use*	Imipramine 50 mg once (cycle day not indicated)	COC (any type with EE≤50 mcg)	$t_{1/2}$, AUC, clearance, of imipramine	Imipramine parameters for OCP users vs. non-users: ↑ AUC by 104% (415 ng/mL h.−1 vs 203) ↓ oral clearance (2322 ml/min vs 4649 ml/min) No change in oral elimination $t_{1/2}$	Steady sate of perpetrator drug achieved	Unclear how COC use was measured with likely a range of doses and formulations used Poor sample size and one time imipramine dose	Poor
Edelbroek, P. M. 1987. Funding source not stated	PK Parallel	Women aged 18–43 with bulimia (at least 5 binges per week and at least 75% of ideal body weight) *5 OC users* *13 non-OC users*	Amitriptyline 25 mg for 6 weeks	OC use (any type)	Plasma concentration of amitriptyline and metabolites (NT, Z-10-OH-NT and E-10-OH-NT) (drawn on days 15, 36 and 57)	For day 36 levels OC users had: *89.7% higher* mean amitriptyline concentration 74 vs 39 mcg/L; p-0.0007 *100% higher* [Z-10-OH-NT] 14 vs. 7 mcg/L; p=.02	Only study with amitriptyline	Women with bulimia. However when looking at PK for d-d interaction may not be relevant. Inadequate sample size (n=5 for OC user arm) Wide range of OC types and doses presumably used. OC exposure assessment not reported. Limited relevance of PK parameters since only one time concentrations given. Unclear why statistics performed only on day 36 values	Poor

C_{max}, Maximum concentration; GPCR, general practitioner clinical research group; NT, nortriptyline; $t_{1/2}$, half life; Z-10-OH-NT, Z-10-hydroxynortriptyline.

Table 3

Evidence table for use of bupropion and atypical anti-psychotics with hormonal contraception

Author, year, funding source	Design	Study population	Exposure Psychotropic drug	Exposure Contraceptive	Outcomes	Outcomes Results	Strengths	Limitations	Quality
Bupropion									
Palovaara, S. 2003 GlaskoSmith Kline provided bupropion	PK Randomized balanced crossover	Healthy women aged 20–25, BMI 18–27 (n=12) No OC use for≤2 months	Bupropion (150 mg) given on day 0 and day 10	EE (30 mcg)/ desogestrel (150 mcg) for 10 days	Plasma concentrations of bupropion and metabolites, AUC, C_{max}, t_{max}	COC vs. Non-OC AUC (bup)- ↓ *19%* 0.72 vs. 0.89 mcg/ml.h (p<.001) C_{max} (bup)- *no change* 76 vs 80 ng/ml (p=.59) AUC (Hydroxybup) ↓ *31%* 16 vs 11 mcg/ml. h (p<.001) C_{max} (hydroxybup) ↓ *20%* 426 vs 335 ng/ml (p=.009)	Crossover design, single COC given, appropriate PK parameter measured and evaluated known active metabolite	Unable to distinguish if the estrogen or progestin component was associated with the changes seen	Good
Atypical Antipsychotics									
Muirhead, G. J. 2000 Pfizer Central Research	PK with some clinical info Double blinded, placebo controlled two way cross-over	Healthy women aged 22–39, non-smokers, within 20% ideal body weight, taking OCPs for ≥3 months (n=19)	COC for 21 days; day 1–7 COC alone and day 8–15 COC + placebo or ziprasidone 7 day washout	EE 30 mcg/LNG 150 mcg	AUC(0,24 h), C_{max} and t_{max} for EE and LNG on cycle day 15 -adverse events, bleeding diaries	EE (*no change*) Ratio for COC/placebo AUC: 99.3% (93.9, 105.1) C_{max}: 93.9 (85.6, 103) *t*max (h); difference 0.6 (−0.2, 1.3) LNG Ratio for COC/ placebo AUC: 97.8% (92.8, 103) C_{max}: 92.7 (84.5, 101.8) t_{max} (h); *difference 0.6* (0.1, 1.3) -Overall COC +ziprasidone did “not produce any clinically significant adverse effects” - shortened menstrual cycle for 1 subject during ziprasidone arm and 1 subject with irregular bleeding during placebo arm	Crossover design, single COC given, appropriate PK parameter measured. Supervised administration of drugs on 13 of 21 days	No ziprasidone levels determined	Good

Author, year, funding source	Design	Study population	Exposure Psychotropic drug	Exposure Contraceptive	Outcomes	Outcomes Results	Strengths	Limitations	Quality
Haslemo, T. 2011 Funding not s tated	PK Parallel	Women ages 18–45 on olanzapine at one routine therapeutic drug monitoring center *n*=149 *10 Estrogen containing contraceptive (ECC) users 10 Progestogen-based contraceptive (PBC) users 129 non-users*	Olanzapine (2.5–30 mg)	Estrogen containing contraceptives or progestin-based contraceptives	Dose-adjusted serum [olanzapine] and [N-desmethylolanzapine] (metabolite) (C:D ratio) one time measurement 10–30 h after last drug dose	C:D ratios (ECC/PBC/ non-users) Olanzapine: *No change* 7.83/7.8/7.67 (p=.99) Metabolite: *ECC* ↓ 33% *PBC* No change 1.3/2.2/1.95 (p=.033) Large inter-individual variability for both C:D ratios for olanzapine and metabolite	Separated estrogen containing contraceptives from progestin only ones	Large range of Olanzapine doses however was dose-adjusted Sample size small one time measurement, broad timing for blood draw, Range of doses and formulations for contraceptives. Unclear role of metabolite thus hard to interpret results	Fair
Chiu Y. 2014. Sunovion Pharmaceuticals inc.	PK Placebo controlled double blind, two-way crossover	Healthy female volunteers, age 18–40 years (*n*=17)	lurasidone 40 mg or placebo once daily on days 12–21 then crossover	COC 35 mcg ethinyl estradiol and 180–250 mcg norgestimate daily	C_{max} and AUC (0–24) of what?	Geometric mean ratio (90% CI) EE-*no change* AUC: 1.12 (1.06–1.18) C_{max} 1.08 (0.97–1.21) Norgestimate no change AUC: 1.03 (0.92–1.15) C_{max} 0.98 (0.87–1.10) 1 adverse event (dysmenorrhea)	Crossover design, single COC given, appropriate PK parameter measured	Only 17 completed study out of 23 enrolled (no explanation)	Good

C_{max}, Maximum concentration; ECC, estrogen containing contraceptive; PBC, progestin based contraceptive; $t_{1/2}$, half life; t_{max}, time to maximum concentration.

Table 4

Evidence table for use of oral benzodiazepines with hormonal contraceptives

Author, year, funding source	Design	Study population	Exposure Psychotropic drug	Exposure Contraceptive	Outcomes	Results	Strengths	Limitations	Quality
Clinical studies for oral benzodiazepines									
Kroboth 1985 Upjohn Company	Secondary outcome of parallel PK study	Women on COCs (n=19) vs not taking COCs (n=21) (matched by age, weight, smoking status)	Single oral doses of either: triazolam 0.5 mg and temazepam 30 or alprazolam 1 mg and lorazepam 2 mg, dosed 28 days apart	COCs with 35 mcg EE or less	Psychomotor impairment, sleepiness scale, nurse rated sedation scale, memory (recall/ recognition)	ALP, LOR, and TRZ produced greater psychomotor performance impairment in the OC users. No difference in sedation or memory.		Not blinded Same study as Stoehr et al., reported number of subjects inverted for OC/ control groups Not powered for clinical outcomes	Fair
Somos 1990 Funding not stated	Observational	Healthy women on COCs (n=72) who also took a concurrent sedative or hypnotic	Diazepam (5 mg), nitrazepam (5–10 mg), chlordiazepoxide (5 mg), meprobamate (200 mg) taken consistently over 14 days to 2 months	COCs with 50 mcg EE or less and LNG	Breakthrough bleeding (BTB), pregnancy	BTB in 36.1% of women, no pregnancies. Most BTB occurred with chlordiazepoxide (12/19) and meprobamate (11/17). One of 15 women on diazepam and 2/21 on nitrazepam experienced BTB.		Did not control dose or duration of use of benzodiazepines. No statistics performed. Follow up duration not clear. Baseline bleeding retrospective and descriptive limiting ability to compare outcomes with/ without benzo	Poor
PK studies for oral benzodiazepines									
Abernathy 1983 US Public Health Service	PK Parallel	Healthy women on COC (n=17) vs not on COCs (n=14) (age 19–37; matched by smoking)	Single dose of 30 mg oral oxazepam (cycle day not specified)	COCs with 50 mcg EE or less	Oxazepam VD, $t_{1/2}$ clearance, free fraction in plasma over 48 h	No significant difference in any measures		No report of AUC, t_{max}, C_{max}. OC formulation varied and unspecified.	Fair
Patwardhan 1983 Veterans Administration and NIH	PK Parallel	Healthy women on COCs (n=5) vs not taking COCs (n=6) (age 21–33)	Single dose of 45 mg oral oxazepam (cycle day not specified)	Norethindrone 1 mg and EE 50 mcg	Oxazepam Vd, $t_{1/2}$, clearance over 48 h	OZM-$t_{1/2}$ ↓NS Clearance ↑ 157% (p<.01) Vd higher (NS)		No report of AUC, t_{max}, C_{max} Small sample size	Fair
Stoehr 1984 Upjohn Company	PK Parallel	Women on COCs (n=19) vs not taking COCs (n=21) (matched by age, weight, smoking status)	Single oral doses of either: triazolam 0.5 mg and temazepam 30 or alprazolam 1 mg and lorazepam 2 mg, dosed 28 days apart	COCs with 35 mcg EE or less	Benzodiaz. Vd, $t_{1/2}$, AUC, elimination constant, clearance, C_{max}, t_{max}	No changes except where noted *TRZ*: no change *TMZ*: AUC down from 9600 ng/ml*h. control to 5840 ng/ml*h. OCs, p<.05), elimination constant up from 0.052 h^{-1} control to 0.087 h^{-1} OCs, p<.005.	Included AUC, t_{max}, C_{max} Groups matched		Fair

Author, year, funding source	Design	Study population	Exposure Psychotropic drug	Exposure Contraceptive	Outcomes	Results	Strengths	Limitations	Quality
						ALP: AUC control-241 ng/ml*h. COC-326 ng/ml*h. p<.01, elimination constant Control-9.6 h^{-1} COC-12.4 h^{-1}, p<.005. *LOR*: elimination constant Control-0.042 h^{-1} COC-0.054 h^{-1}, p<.025.			
Scavone 1988 US Department of HHS	PK Parallel	Healthy women on COCs (n=16) vs not taking COCs (n=23) (matched by age and weight,)	Single dose of 1 mg oral alprazolam (cycle day not specified)	COCs with 50 mcg EE or less	Alprazolam AUC, $t_{1/2}$, Vd, free fraction, clearance over 48 h	No significant difference in AUC, $t_{1/2}$, Vd, clearance. Free fraction (% unbound) slightly higher in COC users.		C_{max}, t_{max} not reported	Fair

ALP, alprazolam; C_{max}, maximum concentration; LOR, lorazepam; $t_{1/2}$, half life; t_{max}, time to maximum concentration; TMZ, temazepam; TRZ, triazolam; Vd, volume of distribution.