Open Access Journal of Contraception

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Comparison of Dermatologic and Neuropsychological Side Effects of Oral Contraceptives, 2016–2020

Joseph Visingardi[1,*], Paul J Feustel[2,*], Rachel Flink-Bochacki[3,*], Cassandra Denefrio[3,*]

[1]Internal Medicine, Albany Medical Center, Albany, NY, USA; [2]Neuroscience and Experimental Therapeutics, Albany Medical College, Albany, NY, USA; [3]Obstetrics and Gynecology, Albany Medical Center, Albany, NY, USA

*These authors contributed equally to this work

Correspondence: Joseph Visingardi, Email visingj@amc.edu

Purpose: Many patients seek a contraceptive medication that lessens symptom burden of comorbid conditions. To date, there have been limited studies investigating how oral contraceptives compare in rates of skin and mood-related side effects. The goal of this study was to compare rates of dermatological and neuropsychological side effects with various oral contraceptive formulations.

Patients and Methods: We utilized FDA Adverse Event Reporting System (FAERS) and Medical Expenditure Panel Survey (MEPS) data to compare rates of reported subjective side effects for oral contraception pills from 2016 to 2020, including acne, migraine, anxiety, and depression. Ethinyl estradiol/Norethindrone was used as the reference pill, as it is the oldest and the most prescribed combination oral contraceptive.

Results: Pills with drospirenone had higher rates of acne, migraine, depression, and anxiety. Acne was also greater with levonorgestrel and norgestimate pills, and anxiety was greater with levonorgestrel combination pills and norethindrone alone.

Conclusion: Oral contraceptive formulation may affect dermatologic and neuropsychological symptoms. Multiple progestins may impact rates of acne and anxiety, with fewer effects on depression and migraine headaches. This knowledge may allow for the personalization of medication selection based on the patients' other co-morbid conditions.

Keywords: contraception, combined oral contraceptives, side effects, psychological, acne, migraine, anxiety, depression

Introduction

Oral contraceptives have been shown to be safe and efficacious for more than half a century, with the first oral contraceptive being approved by the Food and Drug Administration (FDA) in 1960. As with many medications, side effects noted came through the study of medication use in the general population. Despite long term use and myriad options for oral contraceptives, there is still much unknown about the side effect profile, particularly when comparing formulations.[1] Each medication in this class has nuances which may prompt a prescriber to favor a particular formulation. However, there are limited data on head-to-head comparisons of side effects between oral contraceptive medications, particularly in dermatologic and neuropsychological manifestations, which are more subjective and less likely to be accurately captured in medical records.[2]

Research indicates that 4–10% of COC users report mood-related issues such as increased anxiety, irritability, or depressed mood.[3] In some US-based analyses, a subset of oral contraceptive users met criteria for major depression: for example, a study using NHANES data (2005–2012) found a 4.6% prevalence of major depressive symptoms among current OCP users (age 18–55) compared with higher rates in former or never users.[4]

These findings coexist with conflicting evidence. Some epidemiological work suggests that OC users may have lower levels of depressive symptoms compared with non-users, potentially reflecting selection bias, prior mental health status, or other confounding factors.[5] Other studies highlight the difficulty in establishing causality due to methodological

https://doi.org/10.2147/OAJC.S556852
Received: 29 July 2025
Accepted: 21 January 2026
Published: 17 February 2026

limitations, including small sample sizes, non-randomized designs, or focus on single contraceptive formulations.[3,6,7] This contradictory landscape—where some users experience worsening of acne or mood, while others report improvements or no change—underscores the complexity of hormonal contraception's effects and the inadequacy of current data to draw definitive conclusions.

Given these ambiguities and methodological gaps, the present study seeks to examine multiple COC formulations in a large and diverse sample, focusing specifically on both dermatological and neurological/psychiatric outcomes. By doing so, we aim to provide a more comprehensive assessment of the prevalence, severity, and real-world impact of side effects such as acne, migraines, anxiety, and depression.

Materials and Methods

We sourced data from the FDA's Adverse Event Reporting System (FAERS) to determine the incidence of side effects for each medication in the United States.[8] The Medical Expenditure Panel Survey (MEPS) was used to determine the total number of patients prescribed each medication.[9] Both databases are upkept by the United States government and data was analyzed from January 2016 to December 2020. Incidence rates of each side effect for each medication were calculated and comparisons made by utilizing binary logistic regression to determine odds ratios.

We selected ethinyl estradiol (EE)/norethindrone (NET) as our reference medication, as the most long-standing oral contraceptive, containing a first-generation progestin.[10] We queried both databases for medication brand and generic names. Medications investigated include EE/levonorgestrel (LNG), EE/desogestrel (DSG), EE/norgestimate (NRG), EE/drospirenone (DRSP), norethindrone-only pill (NET) and the reference EE/NET. All patients receiving prescriptions for oral contraceptives were included, regardless of indication. Table S1 shows the progestin generation, brand names for each formulation included, along with total prescriptions during the study period. Dermatologic and neuropsychological outcomes included acne, migraine, anxiety, and depression. Side effects were reported by either healthcare providers or the patient. We determined side effect rate using reports over total prescriptions, subsequently calculating odds ratios. Significance was determined at $p<0.05$. We used Minitab (v19) and R (version 4.0.3; https://www.r-project.org/) statistical software for analysis.

Results

Table 1 shows the rate of dermatologic and neuropsychological side effects for each medication formulation per 100,000 users. Statistically significant higher relative rates of acne were seen with EE/LNG (OR 1.6), EE/NRG (OR 2.3), and EE/DRSP (OR 2.8). Higher rates of migraine were seen with EE/DRSP (OR 2.7). Anxiety was noted at higher rates with EE/LNG (OR 1.7) and EE/DSG (OR 2.0), and lower rates with NET alone (OR 0.3). Depression was noted at higher rates with EE/DRSP (OR 3.2).

Table 1 Rate of Side Effects per Medication Formulation with Comparison to Reference Group Ethinyl Estradiol (EE)/Norethindrone Acetate (NETA)

Side Effect/ Medication	Rate/100,000 Users	SD (Standard Deviation)	p-value vs EE/NETA	OR (Odds Ratio)	CI (Confidence Interval)
Acne					
EE/NETA	0.350	0.0904	Reference	Reference	Reference
EE/LNG	0.561	0.302	***0.025***	1.6093	(1.0627, 2.4371)
EE/DSG	0.263	0.1868	0.257	0.6962	(0.3725, 1.3013)
EE/NRG	0.811	0.458	<0.001	2.2897	(1.6385, 3.1998)
EE/DRSP	1.048	0.357	<0.001	2.7996	(1.9167, 4.0900)
NET	0.208	0.1181	0.063	0.5115	(0.2526, 1.0358)

(*Continued*)

Table 1 (Continued).

Side Effect/ Medication	Rate/100,000 Users	SD (Standard Deviation)	p-value vs EE/NETA	OR (Odds Ratio)	CI (Confidence Interval)
Migraine					
EE/NETA	0.376	0.1776	Reference	Reference	Reference
EE/LNG	0.530	0.2166	0.114	1.4043	(0.9218, 2.1391)
EE/DSG	0.384	0.261	0.968	0.9893	(0.5824, 1.6807)
EE/NRG	0.356	0.2057	0.787	0.9461	(0.6334, 1.4134)
EE/DRSP	1.050	0.289	<0.001	2.7027	(1.8626, 3.9212)
NET	0.731	0.727	0.075	1.5076	(0.9590, 2.3698)
Anxiety					
EE/NETA	1.338	1.625	Reference	Reference	Reference
EE/LNG	2.190	3.59	<0.001	1.7353	(1.4044, 2.1441)
EE/DSG	2.660	5.28	<0.001	1.9679	(1.5735, 2.4613)
EE/NRG	1.700	2.41	0.056	1.2162	(0.9953, 1.4862)
EE/DRSP	1.455	0.754	0.35	1.1325	(0.8726, 1.4697)
NET	0.498	0.273	<0.001	0.3393	(0.2184, 0.5270)
Depression					
EE/NETA	0.466	0.272	Reference	Reference	Reference
EE/LNG	0.638	0.228	0.121	1.3469	(0.9242, 1.9634)
EE/DSG	0.297	0.0836	0.081	0.6008	(0.3392, 1.0644)
EE/NRG	0.639	0.588	0.081	1.3334	(0.9650, 1.8424)
EE/DRSP	1.541	0.463	<0.01	3.1655	(2.3070, 4.3430)
NET	0.687	0.475	0.367	1.2190	(0.7929, 1.8746)

Discussion

Acne

Earlier generations of progestins such as the first and second generations tend to be more androgenic, whereas third- and fourth-generation progestins tend to be less androgenic.[10,11] As a result, less acne would be expected with third- and fourth-generation progestins. Despite this, several previous studies demonstrate mixed results.[12] For example, Samanta and Maiti (2022) reported that COCs can either improve or exacerbate acne depending on the formulation, highlighting the contradictory evidence.[13] As expected, desogestrel, a third-generation progestin demonstrated no difference in acne. However, other third- and fourth-generation progestins, drospirenone and norgestimate showed higher reported rates of acne. Drospirenone has been regarded as the least androgenic progestin and even antiandrogenic due to its structural similarity to spironolactone.[10,11,14] The increased rate of acne may be due to increased prescription of drospirenone containing pills for patients with a history of acne. Of note, norethindrone alone showed no difference, signifying that the estrogen product may not have much of an effect on acne, however given the structure of database reporting this may be confounded by selection bias.

Migraine

To date, the characteristics of oral contraceptives which may cause migraines are not fully understood. It is believed that withdrawal of estrogen may contribute to headaches, but this mechanism has not been fully elucidated.[15] In our study, we noted that drospirenone demonstrated increased rates of migraine compared to the reference. This observation can be compared with prior studies worldwide; for example, Ciarcia & Huckins (2024) also report higher migraine rates with drospirenone-containing pills, suggesting that specific progestin components may contribute to neurological side effects. Another proposed mechanism of why this might be is due to drospirenone's mineralocorticoid antagonistic activity that may promote cerebral vasodilation and trigger migraines as a result.[16] All other medications showed no difference. NET alone did not show any difference signifying that the estrogen component may not play as big of a role as was previously thought.

Anxiety

Currently, there is no consensus on progestin's contribution to anxiety symptoms in patients on oral contraceptives.[17] We noticed less anxiety reported with the NET only pill formulation. This may be indicating that the estrogen component may increase anxiety in patients on combined oral contraceptives. Levonorgestrel and desogestrel also showed increased anxiety; the reasons remain unclear, but similar findings have been reported by Jaafar et al (2024), who noted variable anxiety effects depending on formulation and patient baseline characteristics.[18] Further, there was no difference with the drospirenone, which is the only medication approved for premenstrual dysphoric disorder (PMDD).

Depression

Much like anxiety, little is known about what characteristics of oral contraceptives may contribute to depressive symptoms. The only medication FDA approved for PMDD, which contains drospirenone, was associated with higher depression rates in our study.[15] This finding corresponds with prior reports indicating that drospirenone-containing COCs may be associated with depressive symptoms, though confounding by indication and prescription bias with an increase in prescriptions to patients with baseline depression is possible.[16,19]

Limitations

Strengths of this study include its investigation of specific side effects on a population-level. Limitations of the study include reliance on voluntary post-marketing reporting which introduces bias. Although millions of patients are prescribed these medications each year, only a few hundred instances for each of the studied side effects were identified. Also, dose stratification was not completed which may play a role in the rate and severity of each side effect. Likewise, the structure of the database did not allow us to control for confounders such as certain medications being chosen more frequently in a patient with a certain comorbidity along with the inability to control for additional demographic confounders including age and BMI. Newer formulations may be more likely to be prescribed for patients who have had previous side effects from other formulations. Additional studies will be needed to further characterize the post-marketing trends we have identified.

Conclusion

This study supported previous studies on rates of side effects by different oral contraceptive formulations. Selecting medications for a patient when there is a multitude of options often leads to the provider choosing a medication they are most familiar with prescribing. However, better understanding oral contraceptive products, their components, and potential side effect profiles allow for improved personalization of a medication regimen and may help to limit exacerbations of patients' comorbid conditions.

Ethics of Approval

Project Name: Comparison of Dermatologic and Neuropsychological Side Effects of Oral Contraceptives, 2016–2020 Rapid IRB Determination Tool #: R_tED4YNtRsxTYidz.

Albany Medical Centers IRB determined that the above-mentioned project does not meet the regulatory definition of "human subjects" at 45 CFR 46.102(e) and 21 CFR 50.3(g) and 56.102(e) because the research activities do not involve obtaining and studying or analyzing biospecimens or information about living individuals. Therefore, this project has been determined to be not "human subjects" research and does not require further review or approval by the IRB.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

All authors contributed equally to this work in the areas of preparation, collecting data, analyzing data, manuscript preparation and oversight. The author(s) report no conflicts of interest in this work.

References

1. Teal S, Edelman A. Contraception selection, effectiveness, and adverse effects: a review. *JAMA*. 2021;326(24):2507–2518. PMID: 34962522. doi:10.1001/jama.2021.21392
2. Kotb MAM, Ragab HM, Elwan YA, Hussein YHH. Oral contraceptive pills use and adverse effects. *Egypt J Hosp Med*. 2022;86(1):286–290. doi:10.21608/ejhm.2022.211984
3. Lundin C, Danielsson KG, Bixo M, et al. Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle-A double-blind, placebo-controlled randomized trial. *Psychoneuroendocrinology*. 2017;76:135–143. PMID: 27923181. doi:10.1016/j.psyneuen.2016.11.033
4. Gawronska J, Meads C, Smith L, Cao C, Wang N, Walker S. Association of oral contraceptive pill use and depression among US women. *J Affect Disord*. 2024;344:132–140. PMID: 37832730. doi:10.1016/j.jad.2023.10.041
5. Keyes KM, Cheslack-Postava K, Westhoff C, et al. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. *Am J Epidemiol*. 2013;178(9):1378–1388. PMID: 24043440; PMCID: PMC3888252. doi:10.1093/aje/kwt188
6. Segebladh B, Borgström A, Odlind V, Bixo M, Sundström-Poromaa I. Prevalence of psychiatric disorders and premenstrual dysphoric symptoms in patients with experience of adverse mood during treatment with combined oral contraceptives. *Contraception*. 2009;79(1):50–55. PMID: 19041441. doi:10.1016/j.contraception.2008.08.001
7. Cheslack-Postava K, Keyes KM, Lowe SR, Koenen KC. Oral contraceptive use and psychiatric disorders in a nationally representative sample of women. *Arch Womens Ment Health*. 2015;18(1):103–111. PMID: 25113319; PMCID: PMC4308571. doi:10.1007/s00737-014-0453-4
8. FAERS. Available from: https://open.fda.gov/data/faers/#:~:text=The%20FDA%20Adverse%20Event%20Reporting,error%20reports%20submitted%20to%20FDA. Accessed March 25, 2024.
9. Medical Expenditure Panel Survey. Agency for healthcare research and quality. Available from: https://meps.ahrq.gov/mepsweb/. Accessed March 25, 2024.
10. Dragoman MV. The combined oral contraceptive pill – recent developments, risks and benefits. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(6):825–834. PMID: 25028259. doi:10.1016/j.bpobgyn.2014.06.003
11. Sitruk-Ware R, Nath A. The use of newer progestins for contraception. *Contraception*. 2010;82(5):410–417. PMID: 20933114. doi:10.1016/j.contraception.2010.04.004
12. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database Syst Rev*. 2012;(7):CD004425. doi:10.1002/14651858.CD004425.pub6
13. Samanta M, Maiti M. Effects of oral contraceptive pill on female health. *International*. *J Experim Res Rev*. 2022;28:15–24. doi:10.52756/ijerr.2022.v28.003
14. Sitruk-Ware R. Pharmacological profile of progestins. *Maturitas*. 2004;47(4):277–283. PMID: 15063480. doi:10.1016/j.maturitas.2004.01.001
15. Loder EW, Buse DC, Golub JR. Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol*. 2005;193(3 Pt 1):636–649. PMID: 16150254. doi:10.1016/j.ajog.2004.12.089
16. Ciarcia J, Huckins LM. Oral contraceptives and the risk of psychiatric side effects: a review. *Complex Psychiatry*. 2024;10(1–4):36–44. PMID: 39148498; PMCID: PMC11324216. doi:10.1159/000539515
17. Robakis T, Williams KE, Nutkiewicz L, Rasgon NL. Hormonal contraceptives and mood: review of the literature and implications for future research. *Curr Psychiatry Rep*. 2019;21(7):57. PMID: 31172309. doi:10.1007/s11920-019-1034-z
18. Jaafar K, Nabhan E, Daoud R, Nasser Z. Prevalence of anxiety and depression among Lebanese women using oral contraceptives: a cross-sectional study. *BMC Womens Health*. 2024;24(1):47. PMID: 38233890; PMCID: PMC10795317. doi:10.1186/s12905-024-02897-4
19. Johansson T, Vinther Larsen S, Bui M, Ek WE, Karlsson T, Johansson Å. Population-based cohort study of oral contraceptive use and risk of depression. *Epidemiol Psychiatr Sci*. 2023;32:e39. PMID: 37303201; PMCID: PMC10294242. doi:10.1017/S2045796023000525