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Influences of Hormone-Based Contraception on Depressive Symptoms in Premenopausal Women with Major Depression

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Summary

Objective—Hormone-based contraceptives affect mood in healthy women or in women with Premenstrual Dysphoric Disorder. No study has yet examined their association with mood in women with major depressive disorder (MDD). The purpose of this study was to determine whether estrogen-progestin combination or progestin-only contraceptives are associated with depression severity, function and quality of life, or general medical or psychiatric comorbidity in women with MDD.

Methods—This analysis focused on a large population of female outpatients less than 40 years of age with non-psychotic MDD who were treated in 18 primary and 23 psychiatric care settings across the United States, using data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Baseline demographic and clinical information was gathered and compared

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between three groups based on hormonal use: combination (estrogen-progestin)(N=232), progestin-only (N=58), and no hormone treatment (N=948).

Results—Caucasians were significantly more likely to use combined hormone contraception. Women on progestin-only had significantly more general medical comorbidities; greater hypersomnia, weight gain and gastrointestinal symptoms; and worse physical functioning than women in either of the other groups. Those on combined hormone contraception were significantly less depressed than those with no hormone treatment by the 16-item Quick Inventory of Depressive Symptomatology - Self-Rated. The combined hormone group also demonstrated better physical functioning and less obsessive-compulsive disorder comorbidity than either of the other groups.

Conclusions—Synthetic estrogen and progestins may influence depressive and physical symptoms in depressed women.

Keywords

Estradiol; Progesterone; Major Depression; Mood symptoms; Oral contraceptives; Norplant

INTRODUCTION

The use of hormonal forms of contraception is common among women of reproductive age, the most common being a combination of synthetic estrogen (ethinyl estradiol) and synthetic progesterone (progestin). Studies that have examined the effects of these hormone treatments on mood have predominantly been conducted in populations of women with Premenstrual Dysphoric Disorder (PMDD) or healthy women. Early studies using oral contraceptives with high progestin doses reported depression as a possible side effect in normal women in case series and small case-control studies (Nilson and Almgren, 1968; Herzberg et al, 1970; Worsley and Chang, 1978). A large epidemiological-based study found that among women with PMDD who were starting hormone-based contraceptives, most women showed no change in mood, with mood improving in some women and worsening in others (Joffee et al., 2003). This finding in a community-based study agrees with that of an earlier report that hormone-based contraceptives have no effect on mood in this population (Oinonen and Mazmanian, 2002). Studies of "normal women" given hormone-based contraceptives generally report little change in mood (Masse et al., 1998), or they report an altered pattern of mood changes across the menstrual cycle when women on hormone-based contraceptives were compared to those on non-hormone contraceptives (Abraham et al., 2003). A recent placebo controlled study of adolescents given oral contraceptives showed "improvement" in CES-D scores in both placebo treated and oral contraceptive treated adolescents (O'Connell et al, 2007).

In addition to hormone-based contraceptives that include both an estrogen and progestin component, alternative progestin-only forms of contraception are now in use (e.g., Depo-Provera and the Norplant surgical implant), and studies have examined their relationship to mood. In general, progestin-only forms of contraception are longer acting and thus require less compliance burden than daily oral contraceptive administration. In a large multi-site study, Westhoff et al. (1998a) reported that among women who chose Norplant (n = 910), those who dropped out of the study (n = 93) had higher depression scores than those who continued with Norplant. Among those who stayed in the study, depression scores were unchanged after six months. A similar pattern was observed in women who elected to use Depo-Provera (n = 495) (Westhoff et al., 1998b); the women who dropped out (n = 218) had higher depression scores than those who remained on Depo-Provera. The depression scores of women who remained on Depo-Provera showed minimal change over one year. A randomized placebo-controlled trial of the progestin-only contraceptive norethisterone enanthate in 180 postpartum women found significant increases in the Montgomery Asberg and Edinburgh Postnatal Depression

Scales (Lawrie et al., 1998). Thus, there is some literature suggesting that progestin-only forms of contraceptive may worsen mood in women who are susceptible to depression.

Despite these findings of the effects of hormone-based contraceptives on mood, no studies have examined the effects of these hormonal treatments on the symptoms of major depression. Studies in non-human primates have found that the main estrogen in humans, estradiol, modulates brain serotonin systems at multiple sites including synthesis, reuptake and receptors (Shively et al., 2004). Therefore, synthetic estrogen plus progestin (combined) contraceptives that lead to changes in estrogens could influence brain serotonin systems. Some studies have examined the effects of estradiol on depressed mood in women with altered reproductive hormones such as post-partum depression or depression during the perimenopause and found mood improvements in randomized controlled trials (Gregoire et al, 1996; Schmidt et al, 2000; Soares et al, 2001). However, no beneficial effects of estradiol alone were observed in postmenopausal women with depression (Morrison et al, 2004). These studies utilized estradiol rather than ethinyl estradiol so it is unclear whether similar effects would be observed with combined hormone based contraceptives in normally cycling premenopausal women.

Despite suggestions that hormone-based contraceptives might affect mood, the use of these forms of contraception remain prevalent in reproductive aged women, those who are at the greatest risk for development of depression. The purpose of this study was to examine the association of hormone-based contraceptives with mood in a population of premenopausal women with non-psychotic major depressive disorder (MDD) to determine whether those that use combined hormone contraception, progestin-only contraception, or neither differ in terms of depression severity, function and quality of life, and general medical and psychiatric comorbidity.

METHODS

Overview

This report evaluates a broadly representative clinical sample of outpatients with nonpsychotic MDD enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (www.star-d.org). The rationale and design of STAR*D have been detailed elsewhere (Fava et al., 2003; Rush et al., 2004).

Briefly, the aim of STAR*D was to define prospectively which of several treatments are most effective for outpatients with non-psychotic MDD who had an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s). Eligible and consenting STAR*D enrollees were treated initially (Level 1) with the selective serotonin reuptake inhibitor citalopram. Those who reached remission (defined as a score ≤5 on the 16-item Quick Inventory of Depressive Symptomatology - Clinician-rated [QIDS-C_{16}] [Rush et al., 2003; Trivedi et al., 2004; Rush et al., 2006]) or response (a >50% decrease from the baseline QIDS-C_{16} score) could enter a 12-month naturalistic follow-up phase, though non-remitters were advised to enter the subsequent randomized controlled trials which offered a total of four additional possible levels of treatment.

The STAR*D infrastructure included the National Coordinating Center in Dallas, the Data Coordinating Center in Pittsburgh, and 18 primary care and 23 specialty (psychiatric) care clinical settings. The institutional review boards at the National Coordinating Center, the Data Coordinating Center, Regional Centers and Clinical Sites, and the Data Safety Monitoring Board of the National Institute of Mental Health (NIMH; Bethesda, MD) approved and monitored the study protocol.

Clinical Research Coordinators (CRCs) located at the clinical sites were trained and certified in implementing the treatment protocol and in data collection methods (screening, application of inclusion and exclusion criteria, collecting clinical data). Additionally they administered some of the clinician-rated instruments, ensured completion of the self-rated instruments and acted as liaison between the Clinical Sites and the Regional, National and Data Coordinating Centers.

Trained Research Outcomes Assessors (ROAs), who were masked to treatment and were not located at any clinical site, collected outcome data via telephone interviews with participants. Additionally, an automated telephone-based Interactive Voice Response (IVR) system obtained additional outcome data from participants (Kobak et al., 1999).

Study Population

From July 2001 through April 2004, STAR*D enrolled outpatients 18-75 years of age with a diagnosis of nonpsychotic MDD. The present study sample was identified from 4041 consecutive participants enrolled in STAR*D (Fava et al., 2003; Rush et al., 2004). All risks, benefits and adverse events associated with the STAR*D trial were explained to potential participants, who provided written informed consent prior to study participation.

Only self-declared outpatients seeking routine medical or psychiatric treatment were eligible for study participation; recruiting via advertisements was not permitted. Broad inclusion and minimal exclusion criteria were used to ensure a representative sample. Patients with a score ≥14 (moderate intensity) on the CRC-rated 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960; Hamilton, 1967) were eligible. Those with bipolar disorder or psychotic symptoms (lifetime) were excluded, as were those with a current primary diagnosis of obsessive-compulsive or eating disorders, substance abuse/dependence or suicide risk requiring inpatient care, non-response to an adequate treatment trial of any medication used in the first two treatment steps of the protocol during the present episode of MDD, or a seizure disorder or other general medical condition contraindicating medications used in the first two treatment steps. All other psychiatric and general medical comorbidities were allowed. Patients who were pregnant, breast-feeding or planning to conceive in the nine months subsequent to study entry were excluded.

The population for this analysis was comprised of pre-menopausal women (defined as < 40 years of age) on combined hormone contraception (N=232), progestin- only (N=58) or no reproductive hormonal medication (N=948) (Figure 1) using the baseline (pre-treatment) assessments. A medication log was completed at each clinic visit. Study subjects recorded any medication they were taking since the past visit, including the start and end date and the indication. Using this log, medications were classified as to hormone content and type by 4 raters (EAY, SGK and ATH, JB). All 4 individuals had to agree on the classification of the medication or the subject was excluded from analysis.

Assessments

The clinically established diagnosis of non-psychotic MDD was confirmed by a checklist using Diagnostic and Statistical Manual, 4th ed. (DSM-IV) criteria (American Psychiatric Association, 1994). At baseline, the CRCs collected standard demographic information, self-reported psychiatric history (including an assessment of suicidality) and severity of depressive symptoms as assessed by the $HRSD_{17}$ and the QIDS-C_{16}. The CRC administered the Cumulative Illness Rating Scale (CIRS), a 14-item interviewer-administered scale that gauges the severity/morbidity of general medical conditions (GMCs) relevant to different organ systems (Linn et al., 1968; Miller et al., 1992). The CIRS generates three scores: Categories Endorsed indicates the number of the 14 possible comorbid GMCs endorsed by the participant,

Severity Index is the average severity score of the domains endorsed, and Total Severity is the number of categories endorsed multiplied by the average severity.

Additionally, each participant completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Zimmerman and Mattia, 1999). This self-report instrument is used to determine the presence of comorbid psychiatric disorders. The total number of symptom items relevant to each disorder is calculated. Then, based on a 90% specificity threshold, the relevant Axis I disorder is declared to be present or absent (Rush *et al.* submitted).

The ROAs used a telephone interview to collect the $HRSD_{17}$, as well as the 30-item Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$) (Rush et al., 1996; Rush et al., 2000) which uses unconfounded items to measure both core criterion diagnostic symptoms and associated symptoms of depression. The $IDS\text{-}C_{30}$ was used to determine the presence of the atypical (Novic et al, 2005) and melancholic (Kahn et al, 2006) features of depression, and the HRSD17 was used to define the presence of the anxious features of depression (Fava et al, 2004).

A briefer 16-item depression severity scale, the Quick Inventory of Depressive Symptomatology - Self-Report ($QIDS\text{-}SR_{16}$) (Trivedi et al., 1992; Rush et al., 2003) was also completed. The $QIDS\text{-}SR_{16}$ rates the nine criterion symptom domains (range 0-27) needed to diagnose a major depressive episode (MDE) by DSM-IV.

The IVR collected health perceptions by the 12-Item Short Form Health Survey (SF-12) (Ware et al., 1996; Sugar et al., 1998), quality of life by the Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993) which assesses the degree of enjoyment and satisfaction experienced by participants in various areas of daily functioning, and the 5-item Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002) which captures the participant's report of daily function.

Statistical Methods

Comparisons of pre-menopausal women on combined hormone contraception, progesterone-only contraception and no reproductive hormonal contraception were conducted for demographic, clinical, and psychosocial characteristics, depressive symptoms, and psychiatric co-morbidities. Due to missing data, the sample size varied across comparisons.

Analyses are presented both unadjusted and adjusted for age and years of schooling. The association between discrete variables and hormonal status was first tested using the chi-square test and subsequently adjusted for age and years of schooling (or age, years of schooling, and severity of depression as measured by the IDS-C30 in the case of the depression symptoms) via logistic regression analysis for dichotomous variables and multinomial regression for discrete variables with three or more levels. The association between continuous variables and hormonal status was initially tested using the Kruskal-Wallis procedure, and subsequently adjusted for age and years of schooling by means of a generalized linear modeling procedure.

An association was considered statistically significant at $p < 0.05$. Post-hoc testing was conducted for any association revealed to be significant in the adjusted analysis. A Bonferroni correction was applied to all post-hoc comparisons, with a $p < 0.0167$ indicating a statistically significant pairwise comparison.

RESULTS

Table 1 shows the demographic data and the results of comparisons made between the three groups: premenopausal women on combination estrogen and progestin based contraceptives (n=232), those on progestin-only based contraceptives (n=58) and those on no hormonal

contraceptives (n=948). The combination hormone group had a significantly larger proportion of Caucasians than either of the other two groups. The combination group also was younger with more years of education. Subsequent analyses were adjusted for age and education due to differences in these factors between the combination group and the other groups.

Table 2 shows depression clinical characteristics and severity ratings and their association with contraceptive status, as well as post-hoc comparisons made between groups. The combination hormone group showed significantly less depression severity than the non-hormone group on the $HRSD_{17}$, $IDS\text{-}C_{30}$ and $QIDS\text{-}SR_{16}$, though only the $QIDS\text{-}SR_{16}$ result was significant after adjustment for age and education. The combination hormone group also demonstrated significantly better overall functioning compared to the non-hormone group on the Q-LES-Q, WSAS and SF12 physical, though only the SF-12 physical comparison remained significant compared to both of the other groups after adjustment. Women on progestin-only-based contraceptives showed higher medical comorbidity on the CIRS but a better mental functioning (SF-12 mental) than either the combination hormone group or the non-hormone group. No differences were seen in depression subtypes (i.e., atypical vs. melancholic vs. anxious) among the three groups.

The presence of depressive symptoms by contraceptive status and comparisons between groups are shown in Table 3. Women in both hormone groups were more likely to show hypersomnia compared to the non-hormone group. Women in the progestin-only group were significantly more likely to show increased appetite, weight gain and gastrointestinal symptoms than those in the non-hormone group. Adjustment did not affect the findings for weight gain or gastrointestinal symptoms though the significant findings for appetite increase were lost after adjustment. Comorbid psychiatric disorders, as measured by the PDSQ are shown in Table 4. Women in the combination group were less likely to show obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) comorbidities than women in the non-hormone group and were less likely to show panic disorder compared to the progestin-only group. After adjustment, only the OCD result remained significant, with the combination group less likely to show OCD than the non-hormone or progestin-only groups.

DISCUSSION

Hormone-based contraceptives are commonly used by women of reproductive age, the age in which recurrent depressive episodes are commonly seen. The large number of participants enrolled into STAR*D enabled us to examine whether there are any systematic differences among premenopausal depressed women using combination hormone-based contraceptives, those using progestin-only based contraceptives (primarily depot Provera or Norplant) and those not taking exogenous reproductive hormones. The data suggest several findings that were expected and one finding that was surprising. Overall, compared to the non-hormone group, women on combination hormone contraception showed less severity of depression, better physical functioning on the SF-12 and fewer comorbid anxiety disorders based on the PDSQ (Table 4), though only the OCD result remained significant after adjustment. However, women on combination hormone contraception showed lower mental function on the SF-12, which is hard to explain given the lesser severity of depression. The combination hormone group also demonstrated better physical functioning compared to the progestin-only group. These findings persisted after correction for age and educational level, which suggests that this may be related to a pharmacological effect of ethinyl estradiol. Basic studies in animals have found that estrogen is an important modulator of brain serotonin systems and that estrogen reduces anxiety in females in a number of anxiety-related tests (Young et al., 2002). Our data are consistent with the possibility that estrogen-containing contraceptives might have similar effects in depressed women. A greater incidence of hypersomnia was observed in the combined group,

which could be related to the progestins which can induce drowsiness in some women (Rupprecht, 2003) in contrast to estrogen that has central nervous system activating effects (Devidze et al, 2006).

The progestin-only group showed more general medical comorbidity and worse physical functioning on the SF-12 than the combined and non-hormone groups. However, the progestin only group showed better mental functioning on the SF-12 compared to either no hormone group or the combined hormone group. The latter finding is hard to interpret based upon known effects of progestins. The progestin-only group also showed increased appetite (unadjusted result) and weight gain. Both Depot-Provera and Norplant list weight gain as a side effect. Consequently, it is not clear if the increased appetite and weight gain are symptoms of depression or secondary to progestin use but the data suggest that the weight gain is secondary to progestins rather than depression. It is also unclear if progestins unopposed by estrogen worsened some pre-existing medical comorbidities or if women with medical illnesses were more likely to be prescribed progestin-only-based contraceptives.

This study had a number of limitations. First, we do not know the relationship, if any, between use of these contraceptive agents and the depressive symptoms. Similar to other reports, it is likely that women who remained on these forms of contraception were those who tolerated them the best, but we collected no data to make this determination. Furthermore, we do not know the reason women were taking these medications. It is possible some women were prescribed these hormones for mood changes. Although we measured several demographic characteristics, other factors that were not measured including smoking history, history of migraine, religious belief, risks for deep venous thrombosis, past history of high blood pressure, or an abusive partner could impact on whether a woman requests and/or is prescribed ongoing oral contraception. These same variables also could impact on the outcome measures employed in this study. Second, we had a small sample size in the progestin-only group. Nonetheless, we examined this group as progestin has been reported to cause mood disturbances. Data on this group are clearly subject to type II errors due to small sample size. Third, a large number of demographic and symptom variables were analyzed, and no correction was made for multiple tests other than in the post-hoc comparison. Thus, the nature of the analyses was clearly exploratory. Despite the exploratory nature of the analysis, the findings fit with other data that have examined the effects of hormone-based contraceptive treatments in general samples of women (i.e., increased sleep and increased appetite). Finally, the findings of higher educational levels in women using combined hormone treatments, which parallels the findings in naturalistic hormone replacement studies, may still influence some of the observed differences. Other differences found among the groups like race and insurance status may have additionally contributed to the findings since this is a naturalistic study and other unmeasured variables may have influenced which women were or were not using hormone based contraceptives.

In summary, our data suggest that women receiving combination hormone-based contraceptives showed less severe depressive symptoms, better overall physical function and a decreased number of comorbid anxiety disorders, findings that may be linked to beneficial effects of ethinyl estradiol. Future prospective studies are needed to determine whether estrogens might improve some aspects of overall functioning in depressed women. Women with major depression who take progestin-only contraception may experience changes in GI symptoms such as overeating and weight gain that influence depressive symptom profiles. Finally, overall effects of hormone based contraception on mood were small and there is no evidence any of these hormone treatments worsened depressive symptoms.

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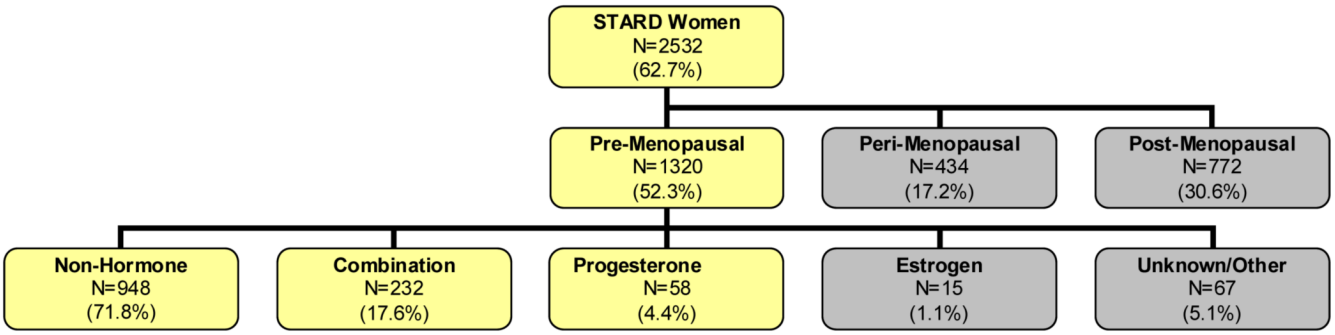

Figure 1.

Diagram of Study Population demonstrating the distribution of subjects. The total sample of women entering STAR*D was 2532. Of these we excluded all women who were perimenopausal or postmenopausal for a sample size of 1320. Some subjects were excluded because of unclear data or use of other hormones such as androgens or androgen antagonists, which would affect reproductive hormones. The total sample size was 1238. The darkened nodes indicate groups not included in the sample

Table 1

Demographic Characteristics: Associations with Hormonal Status

Demographic Characteristics	Contraception Used						Unadjusted p-value	Adjusted OR Combo vs. Non-Hormone	Adjusted OR Progestin vs. Non-Hormone	Adjusted p-value*
	Combo (N=232)		Progestin (N=58)		Non-Hormone (N=948					
	n	%	n	%	N	%				
Race-Caucasian**	185	79.7	40	69.0	656	69.2	**0.0060**	1.62	0.97	**0.0290**
Ethnicity-Hispanic	28	12.1	7	12.0	148	15.6	0.3277	0.91	0.74	0.7291
Employment Status - Employed	168	72.4	34	58.6	589	62.3	**0.0106**	1.38	0.92	0.1458
Marital Status-Married	84	36.2	26	44.8	366	38.7	0.4712	1.15	1.47	0.2921
Insurance										
Private	144	63.7	23	41.1	459	50.4	**0.0014**	1.41	0.77	0.0851
Public	21	9.3	12	21.4	151	16.6		0.83	1.16	
No Insurance	61	27.0	21	37.5	301	33.0				
Setting - Primary Care	74	31.9	26	44.8	326	34.4	0.1792	0.93	0.61	0.1924

	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Age	232	26.5	5.5	58	27.4	4.9	948	29.4	5.88	**<.0001**
Education (Yrs of Schooling)	231	14.4	2.9	58	12.7	3.1	946	13.3	3.00	**<.0001**

Models were adjusted for age and years of schooling. Post-Hoc comparisons were performed on adjusted models where $p < 0.05$ (in bold above).

** Post-hoc comparisons revealed that participants in the combination hormone group were 1.599 times as likely to be Caucasian relative to participants in the non-hormone group (p=0.0103).

Table 2

Clinical Characteristics: Association with Hormonal Status

Characteristics	Contraception Used									p-value	Post-Hoc Comparisons**		
	Combo (N=232)			Progestin (N=58)			Non-Hormone (N=948)				Combo vs. Progesterone	Combo vs. Non-Hormone	Progestin vs. Non-Hormone
	n	Mean	SD	n	Mean	SD	n	Mean	SD				
Age at onset of 1st MDE	232	17.22	6.92	57	18.65	7.02	933	18.96	7.94	**0.0405**			
Age at onset of 1st MDE, Adjusted		18.10			19.36			18.68		0.4214			
Number of MDE Episodes	201	3.37	3.66	51	5.78	8.55	828	4.74	8.65	0.2575			
Number of MDE Episodes, Adjusted		3.53			5.79			4.71		0.1013			
Length of Episode (Months)	231	14.64	29.10	58	18.54	38.63	937	19.74	40.40	0.2604			
Length of Episode (Months) , Adjusted		17.71			18.62			19.01		0.9042			
GIRS total score	232	2.54	2.41	58	3.98	3.06	948	2.97	2.83	**0.0021**			
GIRS total score, Adjusted		2.84			4.00			2.90		**0.0099**	**0.0017**	0.797	**0.0036**
Length of Illness	232	9.36	7.92	57	8.74	6.38	933	10.53	8.00	**0.0469**			
Length of Illness, Adjusted		10.75			9.47			10.15		0.3957			
HRSD17	217	19.51	5.90	50	19.54	5.99	864	20.62	6.49	0.0237			
HRSD17, Adjusted		20.15			19.32			20.47		0.3929			
IDS-C30	214	35.35	10.37	48	37.21	11.37	859	37.33	11.31	**0.0479**			
IDS-C30, Adjusted		36.36			36.91			37.09		0.6978			
QIDS-SR16	232	15.01	4.18	58	16.07	4.49	945	16.43	4.15	**<.0001**			
QIDS-SR16, Adjusted		15.11			15.98			16.40		**0.0002**	0.1647	**<.0001**	0.4462
SF-12 (Mental)	218	23.91	7.66	53	27.33	9.23	850	24.65	8.17	**0.0487**			
SF-12 (Mental) , Adjusted		24.13			27.27			24.61		**0.0423**	**0.0047**	0.4633	0.0285
SF-12 (Physical)	218	55.66	8.74	53	50.57	11.13	850	51.97	10.36	**<.0001**			
SF-12 (Physical) , Adjusted		54.45			50.86			52.25		**0.0072**	**0.0044**	**0.0049**	0.3539
WSAS	218	21.81	8.67	53	22.47	9.58	850	24.08	9.27	**0.0014**			
WSAS, Adjusted		22.35			22.49			23.95		0.0560			
CLESQ	218	44.22	13.64	53	43.72	15.43	850	40.69	15.08	**0.0081**			
CLESQ, Adjusted		43.11			43.72			40.96		0.0940			

	Combo (N=232)		Progestin (N=58)		Non-Hormone (N=948)					
	N	%	n	%	n	%	Unadjusted p-value	Adjusted OR Combo vs. Non Hormone	Adjusted OR Progestin vs. Non-Hormone	Adjusted p-value
Family History of Depression	148	64.3	31	53.5	544	58.0	0.1460	1.28	0.83	0.1920
Attempted Suicide	49	21.1	12	20.7	217	22.9	0.8008	0.99	0.80	0.8128
Chronic Depression	37	16.9	11	19.0	192	20.5	0.3057	0.88	0.95	0.8190
Recurrent Depression	158	73.5	663	75.1	41	75.9	0.8736	0.88	1.07	0.7275
Age of Onset	102	44.0	25	43.9	464	49.7	0.2277	0.90	0.93	0.7975
Anxious Features	90	41.3	21	40.4	420	48.3	0.1186	0.98	0.70	0.4896
Atypical Features	42	19.3	15	28.9	178	20.5				
Melancholic Features	40	18.4	6	11.5	194	22.3	0.1049	0.84	0.45	0.1559

Characteristics	Contraception Used									p-value	Post-Hoc Comparisons**		
	Combo (N=232)			Progestin (N=58)			Non-Hormone (N=948)				Combo vs. Progesterone	Combo vs. Non-Hormone	Progestin vs. Non-Hormone
	n	Mean	SD	n	Mean	SD	n	Mean	SD				

Model adjusted for age and years of schooling.

MDE: Major Depressive Episode, CIRS: Cumulative Illness Rating Scale, HRSD17: 17-item Hamilton Rating Scale for Depression, IDS-C30: 30-item Inventory of Depressive Symptomatology, QIDSSR16: 16-item Quick Inventory of Depressive Symptomatology, SF-12: 12-item Short Form Health Survey, WSAS: Work and Social Adjustment Scale, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire

** Post-Hoc comparisons were performed for adjusted models where $p < 0.05$.

Table 3

Baseline IDS-C30 (ROA): Hormonal Status

		Combo (N=232)				Progesterone (N=58)				Non-Hormone (N=948)						
		Absent		Present		Absent		Present		Absent		Present				
IDS-C30 (ROA) items	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**	**p-value**	**adj OR combo v. non-hormone**	**adj OR prog v. non-hormone**	**adj p-value***
Sleep Onset Insomnia	1140	71	32.6	147	67.4	18	34.6	34	65.4	251	28.9	619	71.1	0.4171	1.00	0.64	0.4192
Mid-Nocturnal Insomnia	1139	48	22.0	170	78.0	10	19.2	42	80.8	184	21.2	685	78.8	0.9018	1.30	1.33	0.3765
Early Morning Insomnia	1141	113	51.8	105	48.2	26	50.0	26	50.0	460	52.8	411	47.2	0.9034	1.44	1.13	0.1063
Hypersomnia	1139	133	61.3	84	38.7	31	60.8	20	39.2	646	74.2	225	25.8	0.0002	1.42	1.69	**0.0387**
Mood-Sad	1141	5	2.3	213	97.7	1	1.9	51	98.2	15	1.7	856	98.3	0.7072	0.51	1.61	0.5435
Mood-Irritable	1141	28	12.8	190	87.2	6	11.5	46	88.5	103	11.8	768	88.2	0.9128	1.13	0.88	0.8462
Mood-Anxious	1141	49	22.5	169	77.5	10	19.2	42	80.8	149	17.1	722	82.9	0.1818	0.73	0.82	0.2837
Reactivity of Mood	1140	52	23.9	166	76.1	15	28.9	37	71.2	223	25.6	647	74.4	0.7318	1.32	0.80	0.2831
Mood Variation	1140	165	76.0	52	24.0	37	71.1	15	28.9	664	76.2	207	23.8	0.7067	1.05	1.43	0.5455
Quality of Mood	1141	56	25.7	162	74.3	15	28.9	37	71.2	214	24.6	657	75.4	0.7590	0.92	0.78	0.7114
Appetite-Decreased	1138	116	53.2	102	46.8	32	61.5	20	38.5	417	48.0	451	52.0	0.0844	0.92	0.54	0.1377
Appetite-Increased	1138	166	76.1	52	23.9	32	61.5	20	38.5	666	76.7	202	23.3	0.0451	0.95	2.07	0.0568
Weight-Decrease	1140	157	72.0	61	28.0	36	70.6	15	29.4	583	66.9	288	33.1	0.3281	0.89	0.75	0.6086
Weight-Increase	1140	171	78.4	47	21.6	29	56.9	22	43.1	652	74.9	219	25.1	0.0060	0.84	2.44	**0.0073**
Concentration/ Decision Making	1141	16	7.3	202	92.7	6	11.5	46	88.5	75	8.6	796	91.4	0.6040	1.23	0.70	0.6066
Outlook-Self	1139	29	13.3	189	86.7	8	15.4	44	84.6	114	13.1	755	86.9	0.8960	0.87	0.68	0.6204
Outlook-Future	1137	51	23.5	166	76.5	16	30.8	36	69.2	189	21.8	679	78.2	0.2974	0.92	0.56	0.2486
Suicidal Ideation	1141	126	57.8	92	42.2	33	63.5	19	36.5	466	53.5	405	46.5	0.2278	0.97	0.53	0.1818
Involvement	1141	34	15.6	184	84.4	9	17.3	43	82.7	91	10.5	780	89.5	0.0477	0.56	0.51	**0.0403**
Energy/Fatigability	1141	8	3.7	210	96.3	6	11.5	46	88.5	62	7.1	809	92.9	0.0665	2.52	0.93	0.0956
Pleasure/Enjoyment	1141	67	30.7	151	69.3	19	36.5	33	63.5	226	25.9	645	74.1	0.1148	0.94	0.49	0.1335
Sexual Interest	1141	68	31.2	150	68.8	12	23.1	40	76.9	287	32.9	584	67.1	0.3152	1.46	1.83	**0.0491**
Psychomotor Slowing	1141	90	41.3	128	58.7	21	40.4	31	59.6	330	37.9	541	62.1	0.6320	0.97	0.89	0.9325
Psychomotor Agitation	1140	87	39.9	131	60.1	22	42.3	30	57.7	313	36.0	557	64.0	0.4046	0.79	0.60	0.1437
Somatic (pain) Complaints	1141	52	23.9	166	76.1	11	21.2	41	78.9	183	21.0	688	79.0	0.6575	0.94	0.98	0.9558
Sympathetic Arousal	1140	86	39.5	132	60.5	19	36.5	33	63.5	298	34.3	572	65.7	0.3511	0.92	0.92	0.8706
Panic/Phobic Symptoms	1136	145	66.8	72	33.2	28	57.1	21	42.9	522	60.0	348	40.0	0.1531	0.80	1.09	0.4417
Gastrointestinal	1141	121	55.5	97	44.5	24	46.1	28	53.9	522	59.9	349	40.1	0.0906	1.61	2.09	**0.0023**
Interpersonal Sensitivity	1141	56	25.7	162	74.3	18	34.6	34	65.4	275	31.6	596	68.4	0.1959	1.26	0.89	0.4249
Leaden Paralysis/ Physical Energy	1141	127	58.3	91	41.7	26	50.0	26	50.0	501	57.5	370	42.5	0.5403	1.18	1.63	0.2345

*Models were adjusted for age, years of schooling and IDS total score at baseline. Post-Hoc comparisons were performed on adjusted models where $p < 0.05$ (in bold above).

**Post-Hoc comparisons revealed that patients in the combination group were 0.34 times as likely to have weight increase relative to those in the progesterone group (p=0.0026), and patients in the progesterone group were 2.4 times as likely to have weight increase relative to those in the non-hormone group (p=0.0048). Regarding gastrointestinal symptoms, patients in the combination group were 1.6 times as likely to develop symptoms relative to the non-hormone group (p=0.0045).

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Table 4

Psychiatric Co-Morbidities (PDSQ): Associations with Contraception Status

Psychiatric Comorbidities Present	Contraception Used						Unadjusted p-value	Adjusted OR Combo vs. Non-Hormone	Adjusted OR Progestin vs. Non-Hormone	Adjusted p-value*
	Combo (N=232)		Progestin (N=58)		Non-Hormone (N=948)					
	n	%	n	%	n	%				
OCD**	17	7.4	8	14.0	155	16.5	0.0020	0.44	0.78	**0.0111**
Panic	25	10.8	14	24.6	138	14.7	0.0270	0.79	1.83	0.0875
Social Phobia	78	33.8	19	33.3	352	37.6	0.4876	0.81	0.73	0.2869
PTSD	30	13.0	10	17.5	202	21.5	0.0135	0.64	0.79	0.1071
Agoraphobia	17	7.4	6	10.5	113	12.1	0.1244	0.70	0.76	0.3849
Alcohol Abuse	16	6.9	7	12.3	88	9.4	0.3497	0.77	1.29	0.5260
Drug abuse	13	5.6	5	8.8	73	7.8	0.4956	0.69	0.97	0.4990
Somatoform	4	1.7	3	5.3	29	3.1	0.3108	0.75	1.73	0.5628
Hypochondriasis	5	2.2	2	3.5	48	5.1	0.1435	0.54	0.63	0.3805
Bulimia	38	16.5	9	15.8	181	19.2	0.5343	0.77	0.75	0.3436
GAD	45	19.5	14	24.6	261	27.8	0.0340	0.71	0.84	0.1759

PDSQ: Psychiatric Diagnostic Screening Questionnaire, OCD: Obsessive-Compulsive Disorder, PTSD: Post-Traumatic Stress Disorder GAD: General Anxiety Disorder

* Models were adjusted for age and years of schooling. Post-Hoc comparisons were performed on adjusted models where $p < 0.05$ (in bold above).

** Post-Hoc comparisons revealed that participants in the combination hormone group were 0.441 times as likely to have OCD relative to participants in the non-hormone group (p-value=0.0027).