Analysis of Adherence, Persistence, and Surgery Among Endometriosis Patients Treated with Leuprolide Acetate Plus Norethindrone Acetate Add-Back Therapy

Ahmed M. Soliman, PhD, MS; Machaon Bonafede, PhD, MPH; Amanda M. Farr, MPH; Jane Castelli-Haley, PhD, MBA; and Craig Winkel, MD, MBA

ABSTRACT

BACKGROUND: Endometriosis affects over 10 million women in the United States. Depot leuprolide acetate (LA), a gonadotropin-releasing hormone agonist, has been used extensively for the treatment of women with endometriosis but is associated with hypoestrogenic symptoms and bone mineral density loss. The concomitant use of add-back therapies, specifically norethindrone acetate (NETA), can alleviate these adverse effects.

OBJECTIVE: To compare adherence to and persistence with LA treatment and time to endometriosis-related surgery among women treated with LA plus NETA and women treated with LA plus other add-back therapies or LA only.

METHODS: This retrospective analysis was conducted using Truven Health MarketScan Commercial Claims and Encounters Database. Women with a diagnosis of endometriosis (ICD-9-CM code 617.xx) who initiated LA (index date) in 2005-2011 were selected for inclusion. Additional requirements were 12 months of continuous enrollment pre- and post-index and no evidence of endometriosis-related surgeries pre-index or up to 30 days post-index; no pre-index use of estrogen or noncontraceptive hormones; and no diagnoses of uterine fibroids, malignant neoplasms, infertility, or pregnancy. Patients were characterized as using NETA; other add-back therapies (estrogens, progestins, or estrogen-progestin combinations); or no add-back therapy. Adherence to and persistence with LA were measured over the 6 months following the index date using outpatient medical and pharmacy claims. Patients were considered adherent if their proportion of days covered was greater than or equal to 0.80. Persistence was operationalized as time to discontinuation, defined as a continuous gap of >60 days without LA on hand. Time to endometriosis-related surgery (laparotomy, laparoscopy, excision/ablation/fulguration, oophorectomy, and hysterectomy) was measured over the 12 months following the index date. Surgeries were identified from inpatient and outpatient medical claims using procedure codes. Outcomes were compared among cohorts using multivariable logistic and Cox proportional hazards regression models controlling for demographics and baseline clinical characteristics.

RESULTS: The final sample included 3,114 women, with a mean age of 36.9 years. The majority of women used LA only with no add-back therapy ($n=1,963$, 63.0%), while 15.1% ($n=470$) used NETA, and 21.9% ($N=681$) used other add-back therapies. During the 6-month follow-up, more patients in the LA plus NETA cohort were adherent to LA therapy compared with LA only (47.2% vs. 31.5%, $P<0.001$), and fewer patients discontinued (37.9% vs. 59.6%, $P<0.001$). Additionally, fewer patients underwent endometriosis-related surgery in the 12 months after LA initiation in the LA plus NETA cohort (12.6% vs. 16.9%, $P=0.021$). In multivariable models, women who initiated LA plus NETA or LA plus other add-back therapies had

a higher likelihood of being adherent to LA than LA only patients (OR = 1.91, 95% CI = 1.55-2.36 and OR = 1.95, 95% CI = 1.63-2.34) and lower likelihood of LA discontinuation (HR = 0.54, 95% CI = 0.46-0.63 and HR = 0.59, 95% CI = 0.52-0.68). NETA patients had a lower surgery rate in the 12-month post-index period compared with other add-back patients (HR = 0.68, 95% CI = 0.50-0.93) or LA only patients (HR = 0.69, 95% CI = 0.52-0.92).

CONCLUSIONS: For women with endometriosis, treatment with LA and concomitant add-back therapies was associated with better adherence to and persistence with LA over the 6 months following initiation, compared with treatment with LA only. The increased adherence and persistence to LA may translate into decreased need for surgical intervention, although fewer endometriosis-related surgeries were only observed in the 12 months following LA initiation for patients using concomitant NETA add-back therapy. These results support an increased and earlier use of NETA add-back therapy among women who initiate LA.

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What is already known about this subject

- Depot leuprolide acetate (LA), a gonadotropin-releasing hormone agonist, has been used extensively for the treatment of women with endometriosis but is associated with menopausal symptoms (hot flashes, vaginal atrophy, and insomnia) and bone mineral density loss.
- The tolerability of LA can be increased with concomitant use of add-back therapies, including norethindrone acetate (NETA).

What this study adds

- This study evaluated adherence to and persistence with LA over the 6 months following initiation among women who initiated LA and used NETA; women who initiated LA and used other add-back therapies; or women who initiated LA only in a large commercial claims database.
- Presence and time to endometriosis-related surgery in the 12 months following LA initiation was also compared among the 3 cohorts.
- Women who initiated add-back therapy were more adherent and persistent to LA therapy, and those who used NETA had lower surgery rates.

Endometriosis, characterized by the presence of extrauterine endometrial-like tissue, is a complex gynecological disease that affects over 10 million women in the United States.¹⁻³ Endometriosis affects at least 6%-10% of reproductive-aged women and is present in approximately 38% of women with infertility and approximately 87% of women with chronic pelvic pain.⁴ Endometriosis can be managed surgically and/or pharmacologically.⁵ Surgical interventions are characterized by high recurrence rates, morbidity, and complication risks, making this approach a formidable challenge.⁶ Endometriosis recurrence rates of up to 50% have been reported in the 5 years following laparoscopic surgery,^{7,8} and many patients undergo multiple surgeries.^{9,10} Current mainstays of noninvasive pharmacologic therapy are oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), progestogens, androgens, and gonadotropin-releasing hormone agonists (GnRHa).¹¹

GnRHa, such as leuprolide acetate (LA), have been used extensively for the treatment of endometriosis, and the microsphere depot formulation of LA administered once a month or once every 3 months provides a more tolerable option than earlier formulations.¹² While 3 to 6 months of treatment with GnRHa has been proven efficacious in improving endometriosis-related symptoms, its long-term use is restricted because of several side effects that include hypoestrogenic symptoms, such as hot flashes, headache, and vaginitis, and associated bone mineral density (BMD) loss.^{7,13} These side effects may be associated with decreased persistence with therapy.¹² Concomitant use of add-back therapy along with GnRHa has been found to improve compliance.¹⁴ Multiple add-back regimens including estrogen, progestins, and norethindrone acetate (NETA) have been demonstrated to prevent BMD loss, without altering the clinical effectiveness of GnRHa.¹⁵⁻¹⁷

In comparison to GnRHa therapy alone, the beneficial impact of adding add-back therapy to GnRHa therapy in reducing the occurrence of osteoporosis and symptoms of postmenopausal syndrome was confirmed in a recently published meta-analysis.¹⁸ NETA, a progestin, is approved by the U.S. Food and Drug Administration (FDA) as add-back therapy to be co-administered with LA for up to 12 months.¹⁹ In clinical trials that assessed the safety and efficacy of LA along with NETA alone or in combination with low-dose conjugated estrogens, the combination of LA plus add-back therapies provided extended pain relief and BMD preservation.¹⁵⁻¹⁷ Similar clinical results regarding reduction in LA-associated BMD loss were reported when LA was given in combination with other add-back agents such as sodium etidronate and low-dose norethindrone and etidronate alone.^{20,21}

Despite higher GnRHa treatment compliance and persistence and a reduced adverse event profile associated with add-back therapy, fewer than 1 in 3 patients treated with GnRHa are estimated to use concomitant add-back therapy.^{12,22} A previously published analysis using claims data from 2002 to 2004 found that use of add-back therapy was associated with

better persistence and compliance to LA.¹² We undertook this retrospective study to extend this area of research by assessing adherence to and persistence with LA treatment among women treated with LA plus NETA; women treated with LA only; and women treated with LA in combination with other hormonal add-back therapies using data reflecting real-world use in more recent years, more clearly defined add-back cohorts, and measurement of adherence and persistence to LA over the initial 6-month period of therapy where use of add-back therapy is not currently mandated per label.¹⁹ An additional objective was to compare time to endometriosis-related surgery among these cohorts of women to determine the potential effect of add-back therapy on surgery rates.

Methods

Data Source

We used data from the Truven Health MarketScan Commercial Claims and Encounters (Commercial) Database from 2004 to 2012. The database contains the pooled health care utilization records of approximately 39.5 million privately insured individuals in the United States.²³ All study data were de-identified and complied with all aspects of the Health Insurance Portability and Accountability Act (HIPAA) and therefore were exempted from institutional review board approval.

Patient Selection

Adult women (aged 18-49 years) with at least 1 claim (outpatient pharmacy or medical) for LA between January 1, 2005, and December 31, 2011, were identified using National Drug Code (NDC) numbers or the Healthcare Common Procedure Coding System (HCPCS) code J1950 for injection, leuprolide acetate (for depot suspension), per 3.75 mg (a separate HCPCS code for the 11.25 mg dose administered every 3 months does not exist). The index date was the first use of LA. Women were required to have at least 1 nondiagnostic medical claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis of endometriosis (617.x) in any position in the 12 months pre-index or up to 60 days post-index. Additionally, patients had to be continuously enrolled with medical and pharmacy benefits for 12 months pre-index (pre-index period) and post-index (follow-up period). Patients were excluded from the study sample if their claims records had codes indicating the following (see Appendix A, available in online article):

- LA claims in the pre-index period.
- Estrogen or noncontraceptive estrogen/progestin combinations claims in the first 11 months of the pre-index period.
- Eligard, Viadur, nondepot LA formulations (e.g., subcutaneous or powder compounding forms), depot LA formulations with a strength of > 11.25 mg or strength of 7.5 mg, or medical claim for 1 mg or 7.5 mg of LA during the study period because these are not indicated for endometriosis treatment.
- Pregnancy-assisting medications during the study period.

- A diagnosis of uterine fibroids, malignant neoplasm of female genitourinary organs, and/or infertility in the pre-index period.
- A claim indicative of pregnancy during the study period.
- A claim for endometriosis-related surgery (laparoscopy, laparotomy, excision/ablation/fulguration, hysterectomy, or oophorectomy) during the pre-index period or within 30 days post-index.

Exposure Measures

Patients were grouped into 3 cohorts: (1) LA with NETA add-back therapy, (2) LA with other add-back therapies, and (3) LA only. These patients were identified using HCPCS on outpatient medical claims and NDC numbers on outpatient pharmacy claims around the index date. Other add-back therapies were defined as estrogens; progestins, including norethindrone; or estrogen/progestin combinations, except hormone-releasing intrauterine devices or implants and depot medroxyprogesterone (see Appendix A for HCPCS codes and Appendix B for a list of medications, available in online article). Patient medical and pharmacy claims were evaluated for the presence of at least two 30-day claims for add-back therapy occurring 30 days before the index date through 45 days after the last use of LA or at least one 90-day claim occurring during that time period. Patients with NETA claims meeting this definition and no claims for other add-back therapies were included in the LA plus NETA cohort. Patients with other add-back claims meeting this definition were included in the LA plus other add-back cohort. Patients who met the definition for NETA add-back therapy but who had claims for other add-back therapies were included in the LA plus other add-back cohort. All other patients were included in the LA only cohort.

Outcome Measures

The 3 study outcomes measured were adherence to index LA therapy, persistence with index LA therapy, and surgery incidence following LA initiation. LA adherence and persistence were calculated using outpatient medical and pharmacy claims. For outpatient medical claims for LA, an estimated duration of prescription supply was adopted from a previous study as follows: 30 days for HCPCS J1950 if the paid amount on the claim was less than \$1,000 and 90 days if the paid amount was \$1,000 or more because a separate HCPCS code for the 11.25 mg dose administered every 3 months does not exist.¹² Adherence was measured using proportion of days covered (PDC), which is defined as the ratio of the total days during follow-up with LA “on hand” to the number of days in the evaluation period.²⁴ Patients with $PDC \geq 0.80$ were considered adherent to LA.^{24,25} Persistence was measured using the LA discontinuation rate. Discontinuation was defined as a gap of at least 60 days after the runout of the previous LA claim based on service dates and days supply/estimated duration of prescription supply. Time to discontinuation was also measured. The third study outcome was endometriosis-related surgery, defined as at least 1 medi-

cal claim with an ICD-9-CM procedure or Current Procedural Terminology (CPT) code for a laparoscopy, laparotomy, other excision/ablation/fulguration, oophorectomy, or hysterectomy during the follow-up period (Appendix A) with an endometriosis diagnosis code on the same day. The presence of and time to first endometriosis-related surgery were described. Adherence and persistence were evaluated during the first 6 months following LA initiation because this is the recommended length of treatment.²⁶ Treatment beyond 6 months necessitates the addition of add-back therapy, according to the FDA.²⁶ Endometriosis-related surgery was measured over the full follow-up period (12 months). The follow-up period is relevant because another previously published analysis measured other LA treatment outcomes, including pelvic pain and BMD, over a 12-month period.¹⁵

Covariates

To account for the multidimensional nature of factors that could affect treatment adherence/persistence, several covariates were captured including demographic and clinical characteristics.²⁷ Baseline demographic characteristics, including age, U.S. Census Bureau geographic region, type of residence (urban/rural) and health insurance plan type, were assessed on the index date. Baseline clinical characteristics, including the Deyo Charlson Comorbidity Index (CCI),²⁸ and comorbid conditions based on the presence of ICD-9-CM diagnosis and CPT procedure codes, and medication use based on NDC numbers and HCPCS codes were assessed during the 12-month pre-index period (Appendix A). Because of the nature of information recorded in claims databases, over-the-counter medication use could not be captured.

Statistical Analysis

All study variables for each study cohort, including demographic and clinical characteristics, medication use, and outcomes, were analyzed descriptively. Categorical variables were compared between cohorts using chi-square tests, whereas continuous variables were compared using t-tests. Multivariable analyses were conducted to compare adherence to and persistence with LA and surgery following LA initiation among the 3 cohorts. The odds of having a $PDC \geq 0.80$ at 6 months post-index were modeled using logistic regression with the add-back therapy cohort (NETA, other, or none) as the independent variable. Cox proportional hazards models were employed to estimate time to LA discontinuation over 6 months post-index and time to endometriosis-related surgery over 12 months post-index with the add-back therapy cohort (NETA, other, or none) as the independent variable. Models controlled for age, insurance plan type, region, urbanicity, CCI, pre-index period anxiety diagnosis, pre-index period depression diagnosis, pre-index period opioid prescription, NSAID prescription, and antidepressant prescription. A *P* value of <0.05 was considered statistically significant.

FIGURE 1 Patient Sample Selection Flowchart

^aPatients who started estrogen or noncontraceptive estrogen/progestin combination within 30 days before index date were not excluded.

^bSurgery includes laparoscopy, laparotomy, other excision/ablation/fulguration, oophorectomy, or hysterectomy.

^cOther forms of leuprolide include nondepot formulations (e.g., subcutaneous or powder compounding forms) or depot formulations with a strength > 11.25 mg or of 7.5 mg or medical claim for 1 mg or 7.5 mg.

LA = leuprolide acetate.

Analysis of Adherence, Persistence, and Surgery Among Endometriosis Patients Treated with Leuprolide Acetate Plus Norethindrone Acetate Add-Back Therapy

TABLE 1 Demographic Characteristics of Women with Endometriosis Who Initiated LA

	LA Plus Add-Back: NETA		LA Plus Add-Back: Other Therapies		LA Only		P Value for LA Plus NETA vs. LA Plus Other	P Value for LA Plus NETA vs. LA Only
	n = 470		n = 681		n = 1,963			
	%	n	%	n	%	n		
Mean [SD] age	36.8	[7.2]	35.2	[7.7]	37.5	[7.2]	<0.001	0.047
Population density								
Urban	81.7	384	80.5	548	80.1	1,572	0.338	0.004
Rural	15.5	73	17.8	121	18.9	371		
Unknown	2.8	13	1.8	12	1.0	20		
Geographic region								
Northeast	18.1	85	12.6	86	15.5	304	0.005	0.007
North Central	23.0	108	29.8	203	25.7	504		
South	42.3	199	40.4	275	43.9	862		
West	13.2	62	15.4	105	13.7	269		
Unknown	3.4	16	1.8	12	1.2	24		
Health plan type								
Comprehensive	3.0	14	4.0	27	4.6	90	0.035	<0.001
EPO	1.5	7	0.4	3	0.6	11		
HMO	23.8	112	21.7	148	23.3	457		
POS	12.3	58	14.5	99	14.1	277		
PPO	46.2	217	51.5	351	50.3	987		
POS with capitation	2.8	13	1.2	8	1.8	36		
CDHP	3.2	15	2.3	16	1.2	23		
HDHP	0.2	1	0.1	1	0.3	5		
Unknown	7.0	33	4.1	28	3.9	77		
Index Year								
2005	6.6	31	14.5	99	11.1	218	<0.001	<0.001
2006	9.8	46	11.6	79	14.3	281		
2007	11.9	56	12.3	84	15.0	294		
2008	10.2	48	12.3	84	12.9	253		
2009	17.9	84	14.8	101	14.9	292		
2010	20.4	96	17.8	121	16.5	324		
2011	23.2	109	16.6	113	15.3	301		

CDHP=consumer-driven health plan; EPO=exclusive provider organization; HDHP=high-deductible health plan; HMO=health maintenance organization; LA=leuprolide acetate; NETA=norethindrone acetate; POS=point-of-service plan; PPO=preferred provider organization; SD=standard deviation.

Results

Study Population

A final sample of 3,114 women with endometriosis who met the inclusion criteria were identified between January 1, 2005, and December 31, 2011. Of these, 470 (15.1%) received LA plus NETA add-back therapy; 681 (21.9%) received LA plus other add-back therapy; and 1,963 (63.0%) received LA only therapy. There were 202 patients who met the NETA definition but had at least 1 claim for other add-back therapy in the 30 days before the index date or in the 45 days after the last LA claim so were included in the other add-back cohort. Complete patient attrition is described in Figure 1.

Baseline Demographics, Clinical Characteristics, and Medication Use

Demographic and pre-index period clinical characteristics are presented in Tables 1 and 2. The mean age across all cohorts

ranged between 35.2 and 37.5 years at index. The majority of patients in the study population resided in urban areas (80.1%-81.7%) and was mostly covered by a preferred provider organization (46.2%-51.5%) or health maintenance organization (21.7%-23.8%) plan. Significant differences were observed in the distribution of patients across geographic regions and in the type of health plans between the cohorts. While the proportion of patients in the index years increased consistently from 2005 to 2011 (6.6%-23.2%) in the LA plus NETA add-back cohort, those in the other cohorts had no defined pattern ($P<0.001$).

In all cohorts, the most prevalent comorbid conditions evaluated were unspecified symptoms of female genital organs (36.7%-42.3%), abdominal/pelvic pain (32.0%-35.3%), dysmenorrhea (12.5%-14.5%), and excessive/frequent menstruation (11.5%-17.3%). The proportion of patients with unspecified symptoms of female genital organs and excessive/frequent menstruation differed significantly between the LA plus NETA

TABLE 2 Clinical Characteristics of Women with Endometriosis Who Initiated LA

	LA Plus Add-Back: NETA		LA Plus Add-Back: Other Therapies		LA Only		P Value for LA Plus NETA vs. LA Plus Other	P Value for LA Plus NETA vs. LA Only
	n = 470		n = 681		n = 1,963			
	%	n	%	n	%	n		
Mean [SD] Deyo CCI	0.2	[0.6]	0.2	[0.6]	0.3	[0.7]	0.932	0.472
Comorbid conditions								
Anxiety	10.0	47	8.7	59	7.4	146	0.441	0.065
Depression	9.6	45	9.8	67	7.8	154	0.882	0.219
Dysmenorrhea	14.5	68	14.2	97	12.5	245	0.915	0.248
Excessive or frequent menstruation	12.6	59	11.5	78	17.3	339	0.571	0.013
Unspecified symptoms of female genital organs	42.3	199	40.5	276	36.7	720	0.539	0.023
Abdominal/pelvic pain	35.3	166	32.9	224	32.0	628	0.393	0.167
Medications								
NSAIDs	40.0	188	40.2	274	36.6	718	0.936	0.168
Opioids	55.5	261	54.5	371	50.4	990	0.724	0.047
Androgens	0.9	4	1.3	9	0.4	7	0.458	0.151
Antidepressants	33.2	156	33.2	226	27.5	539	0.999	0.013
Hormonal contraceptives	27.0	127	64.2	437	22.8	448	<0.001	0.054
Hormone-releasing IUD or implant	0.4	2	0.7	5	0.8	16	0.508	0.376
Depot medroxyprogesterone	4.7	22	2.1	14	4.4	87	0.012	0.815
Other progestins ^a	28.3	133	12.9	88	8.4	164	<0.001	<0.001

^aNoncontraceptive norethindrone, noncontraceptive medroxyprogesterone, and progesterone.

CCI=Charlson Comorbidity Index; IUD=intrauterine device; LA=leuprolide acetate; NETA=norethindrone acetate; NSAIDs=nonsteroidal anti-inflammatory drugs; SD=standard deviation.

add-back therapy cohort and the LA only cohort ($P<0.03$). Opioids (50.4%-55.5%), NSAIDs (36.6%-40.2%), hormonal contraceptives (22.8%-64.2%), and antidepressants (27.5%-33.2%) were the most commonly used medications in the pre-period. Opioid and antidepressant use were significantly more prevalent in the LA plus NETA add-back cohort compared with the LA only cohort ($P<0.05$). The proportion of patients with a claim for hormonal contraceptive was also significantly lower in the LA plus NETA cohort, compared with the LA plus other add-back cohort ($P<0.001$), since hormonal contraceptives use in the 30 days before index was considered in the other add-back category.

Unadjusted Results

Unadjusted results are presented descriptively in Table 3 and Figure 2A and 2B. Over the 6-month post-index period during which LA adherence was measured, women treated with LA plus NETA add-back therapy had significantly ($P<0.001$) higher mean PDC of LA (mean=0.70, standard deviation [SD] 0.27, median=0.78, interquartile range [IQR]=0.49-0.94) compared with patients in the LA only cohort (mean=0.56, [SD] 30], median=0.50, IQR=0.32-0.87). A significantly greater proportion of patients receiving NETA add-back achieved $PDC\geq 0.80$ compared with those without add-back therapy (47.2% vs. 31.5%, $P<0.001$). There was no significant difference between LA plus NETA add-back therapy and LA plus other add-back therapy in therapy terms of mean PDC (LA plus other: mean=0.68,

[SD 0.28], median=0.77, IQR=0.47-0.93) or proportion adherent (LA plus other: 47.9%) The proportion of patients in the LA plus NETA add-back cohort who discontinued LA therapy within 6 months was significantly lower than the LA only cohort (37.9% vs. 59.6%; $P<0.001$). Patients with add-back therapy had longer LA persistence than patients with LA only (mean=139 days [SD 56.0] vs. mean=111 days [SD 62.3], $P<0.001$). Unadjusted time to discontinuation for the 3 cohorts is presented as a Kaplan-Meier curve in Figure 2A; approximately 10% restarted LA after discontinuing within the 6 months following the index date.

Compared with the LA plus NETA add-back therapy cohort, a significantly higher proportion of patients underwent endometriosis-related surgery in the LA only cohort (12.6% vs. 16.9%, $P=0.021$) during the 12-month follow-up period. Hysterectomy was the most common procedure performed (11.7% of entire study population), while laparotomy (0.8% of the entire study population) was rare. Among those who had surgery, patients in the LA plus NETA add-back therapy cohort had significantly longer average time to surgery compared with those in the LA only cohort (mean=185 days [SD 86.4] vs. mean=139 days [SD 94.9], $P=0.001$). Figure 2B presents unadjusted time to surgery. The proportion of patients who had surgery over the 12-month follow-up period was significantly lower for women who were adherent to LA over the first 6 months compared with those who were not adherent (LA plus NETA add-back: 8.6% vs. 16.1%, $P=0.013$; LA plus other add-back: 10.4% vs. 22.8%, $P<0.001$; LA only: 9.7% vs. 20.2%, $P<0.001$). The same

TABLE 3 Adherence and Persistence with LA (6 Months) and Time to Surgery (12 Months) Following LA Initiation Among Women with Endometriosis

	LA Plus Add-Back: NETA		LA Plus Add-Back: Other Therapies		LA Only		P Value for LA Plus NETA vs. LA Plus Other	P Value for LA Plus NETA vs. LA Only
	n = 470		n = 681		n = 1,963			
	%	n	%	n	%	n		
Persistence								
Discontinued during 6 months	37.9	178	40.2	274	59.6	1,169	0.420	<0.001
Restarted LA ^a	18.5	33	13.5	37	7.8	91	0.148	<0.001
Mean [SD] days persistent during 6 months	139	[56.0]	136	[57.4]	111	[62.3]	0.356	<0.001
Adherence								
Mean [SD] PDC during 6 months	0.70	[0.27]	0.68	[0.28]	0.56	[0.30]	0.398	<0.001
PDC≥80	47.2	222	47.9	326	31.5	619	0.193	<0.001
Endometriosis-related surgery								
Had surgery	12.6	59	16.9	115	16.9	332	0.044	0.021
Laparotomy	0.9	4	0.3	2	1.0	19	0.197	0.814
Laparoscopy	3.6	17	5.3	36	4.0	79	0.184	0.684
Other excision/ablation/fulguration	4.5	21	5.4	37	5.2	103	0.462	0.490
Oophorectomy	1.7	8	2.9	20	2.6	51	0.181	0.257
Hysterectomy	8.7	41	12.2	83	12.2	239	0.062	0.035
Mean [SD] days to endometriosis-related surgery, among those who had surgery	185	[86.4]	167	[94.7]	139	[94.9]	0.217	0.001
Mean [SD] days to laparotomy	151	[89.2]	250	[115.3]	169	[111.8]	0.301	0.762
Mean [SD] days to laparoscopy	161	[105.4]	181	[102.4]	155	[92.0]	0.502	0.814
Mean [SD] days to other excision/ablation/fulguration	165	[96.5]	185	[103.9]	146	[96.7]	0.476	0.408
Mean [SD] days to oophorectomy	195	[41.0]	170	[97.7]	144	[79.2]	0.500	0.086
Mean [SD] days to hysterectomy	189	[81.2]	153	[89.3]	137	[94.3]	0.032	0.001

^aDenominator is the number of patients who discontinued LA.

LA = leuprolide acetate; NETA = norethindrone acetate; PDC = proportion of days covered; SD = standard deviation.

trend was observed for women who were persistent compared with those who were nonpersistent to LA over 6 months (LA plus NETA add-back: 9.6% vs. 17.4%, $P=0.013$; LA plus other add-back: 11.3% vs. 25.2%, $P<0.001$; LA only: 11.2% vs. 20.8%, $P<0.001$).

Adjusted Results

Figure 3 contains the multivariable analysis results. Initiating LA plus NETA add-back therapy was associated with increased odds of PDC ≥ 0.80 compared with initiating LA only (odds ratio [OR] = 1.914, 95% confidence interval [CI] = 1.554-2.358, $P<0.001$) when controlling for baseline demographics, clinical characteristics, and concomitant medications. Patients initiating LA plus other add-back therapies also had significantly greater odds of being adherent than LA only patients (OR = 1.952, 95% CI = 1.628-2.340, $P<0.001$). Patients in the LA plus NETA add-back cohort had significantly lower hazards of discontinuation compared with those treated with LA only

(hazard ratio [HR] = 0.538, 95% CI = 0.459-0.631, $P<0.001$), as did patients initiating LA plus other add-back therapies (HR = 0.590, 95% CI = 0.516-0.675, $P<0.001$). There were no significant differences in adherence or persistence when comparing the LA plus NETA cohort with the LA plus other add-back cohort. However, LA plus NETA add-back therapy was associated with decreased hazards of surgery compared with those with LA plus other add-back therapies (HR = 0.681, 95% CI = 0.496-0.934, $P=0.017$) and those treated with LA only (HR = 0.693, 95% CI = 0.523-0.917, $P=0.010$).

Discussion

In a commercially insured population, women with endometriosis treated with LA plus NETA were more likely to be adherent to and persistent with LA for 6 months, compared with patients treated with LA only, and were less likely to have surgery within 12 months, compared with women treated with LA plus other add-back therapies or LA only.

FIGURE 2 Kaplan-Meier Curves for Persistence and Surgery

A. Persistence with LA over 6-Month Follow-up

B. Endometriosis-Related Surgery During 12-Month Follow-up

LA=leuprolide acetate; NETA=norethindrone acetate.

There is also an indication that women who are adherent and persistent to LA have lower rates of surgery. This is currently being explored further in a separate analysis. A recently published meta-analysis confirmed the beneficial effects of adding add-back therapies to GnRHa therapy for endometriosis because add-back therapies reduce the occurrence of osteoporosis and postmenopausal syndrome symptoms compared with GnRHa therapy alone.¹⁸ Use of add-back therapies with a GnRHa, such as LA, is also known to enhance persistence and adherence of LA treatment in patients.^{12,15} Better improvement in the quality of life measures for a longer period of time were also reported in women treated with GnRHa plus add-back therapies, compared with GnRHa or oral contraceptive treatments alone.^{29,30} Since the NETA cohort and other add-back cohort had similar levels of LA adherence and persistence, the difference in surgery risk between the 2 add-back cohorts may be due to use of estrogens by some women in the other add-back cohort. Estrogen use can negate the effects of LA therapy because estrogen stimulates the growth of endometrial tissue.^{31,32} It is important to note that the other add-back cohort is heterogeneous with respect to add-back therapy composition. Therefore, results for that cohort should be interpreted cautiously because individual types of add-back therapy (estrogens, progestins, or combinations thereof) may have different associations with adherence, persistence, and surgery.

Among the add-back therapies, the hormonal profile of NETA has been shown to exhibit strong endometrial

antiproliferative effects and to reduce BMD losses and vasomotor symptoms, such as hot flashes, commonly encountered by women treated with GnRHa.³² The combination of LA and NETA may alleviate the side effects of LA only, resulting in patients staying on the medication for longer periods of time. Although the reduction in number and size of endometriotic lesions was only shown for LA monotherapy,^{26,33} one could speculate that LA's benefit would be likewise present for LA plus add-back therapy, potentially leading to a reduced need for, or a delay in, endometriosis-related surgery. Reducing the need for surgery is expected to be associated with economic savings, given the considerable costs of endometriosis-related surgeries together with rates of complications associated with those procedures.³⁴

This analysis used a large commercial insurance database to describe improved adherence and reduced surgery rates associated with the use of LA and add-back therapy in a database with sufficient sample size and longitudinality to yield robust comparisons. Additionally, the definition of study cohorts produced a clean cohort of patients using LA plus NETA without any other add-back therapies for comparison with LA only patients. The methods employed in this study were influenced by a previous study comparing LA adherence and persistence by Fuldeore et al (2010).¹² This previous analysis was conducted with MarketScan data from 2002 to 2004. Similar to our analysis, the index date was initiation of LA. Evidence of claims for add-back therapy (estrogen, progestin, or

FIGURE 3 Multivariable Adjusted Results for Adherence, Persistence, and Endometriosis-Related Surgery Among Women with Endometriosis Who Initiated LA^a

^aModels controlled for age, plan type, index year, region, urbanicity, Deyo Charlson Comorbidity Index, anxiety diagnosis, depression diagnosis, opioid prescription, NSAID prescription, and antidepressant prescription.

CI=confidence interval; HR=hazard ratio; LA=leuprolide acetate; NETA=norethindrone acetate; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio.

norethindrone) was measured in the 7 days before the index date through 45 days after. Persistence and compliance (measured as medication possession ratio [MPR]) were evaluated over 12 months and found to be better among women with evidence of add-back therapy.¹²

Our analysis varied in several ways. First, the data used in this analysis are reflective of current utilization patterns, compared with the data used in the Fuldeore et al. analysis.¹² Second, we evaluated adherence and persistence over a 6-month period, which is consistent with LA prescribing information for initial endometriosis management. Patients using LA for periods longer than 6 months should be concurrently using add-back therapy per the drug label. We conducted a sensitivity analysis where we measured these outcomes over the 12 months following LA initiation (data not shown), which yielded results similar to the previous analysis of LA and add-back therapy conducted by Fuldeore et al.¹² Over a 12-month period, we found an average PDC of 0.42 for LA plus NETA, 0.40 for LA plus other add-back, and 0.31 for LA only. Fuldeore et al.'s analysis reported an average MPR of 0.43 for LA plus NETA patients, 0.32-0.35 for LA plus other add-back therapy, and 0.32 for LA only.¹² Regarding LA persistence, we found

that patients treated with LA plus NETA persisted on therapy for an average of 5.3 months over the 12-month period, compared with 5.0 months for patients treated with LA plus other add-back therapy and 3.9 for patients treated with LA only. Fuldeore et al. reported times on therapy of 5.8 months, 4.6-5.8 months, and 4.2 months, respectively.¹²

Third, women with endometriosis-related surgery were excluded from our analysis because they may experience effects related to the surgical intervention in combination with LA effects during the follow-up period. Women who underwent surgery within 30 days of initiating LA were also excluded because LA may be used as preparation for surgery rather than as a treatment on its own. Fourth, we employed multivariable models for adherence controlling for demographic and clinical characteristics because previous research has shown that LA adherence is affected by age, while the Fuldeore et al. analysis only modeled persistence in a descriptive manner that did not account for baseline differences between patients.¹²

Limitations

There are limitations to our analysis that merit consideration. First, this study was limited to information contained in an

administrative claims database. Over-the-counter medications are not captured, since they do not generate insurance claims. Symptoms of endometriosis and comorbid conditions may not be captured correctly if the diagnoses were not recorded by health care providers for reimbursement. Another limitation of the current study is that health care claims databases are not designed primarily to capture adverse events (AEs).^{35,36} Thus, certain AEs associated with using LA or undergoing laparoscopy may not be collected if the AE did not result in a diagnosis or procedure on a health care claim. Nonetheless, it must be anticipated that a similar safety profile to that seen in LA's drug labels applies to the study population. Most frequent AEs observed among endometriosis patients are hot flashes, headache, vaginitis, depression/emotional lability, general pain, nausea/vomiting, weight gain or loss, decreased libido, dizziness, acne, and impact on bone health,²⁶ whereas AEs related to undergoing laparoscopy include vascular, intestinal, urinary tract, and nerve injuries.³⁷⁻⁴²

Second, we used the dose defined as per the label and paid amount to estimate day supply for assigning days supply for LA medical claims because doses are not available on medical claims. Third, ICD-9-CM codes do not contain information on endometriosis stage, which may influence treatment choices and outcomes. Endometriosis stage may have differed between the 3 cohorts and could have affected physicians' prescribing patterns.

Fourth, this study design was observational; therefore, causal inference should be drawn cautiously. Physician-prescribing patterns and preferences for pharmacotherapy versus surgical treatments, as well as patient preferences could not be captured. Just as differences in endometriosis stage could have biased the study findings, the inability to adjust for physician and patient preferences may have resulted in uncontrolled confounding. Future research using patient and/or physician surveys should be conducted to assess patient and physician preferences and their relationship with surgery rates.

Finally, the analyses were limited to women with commercial insurance, so the results may not be generalizable to women insured through other mechanisms, such as Medicaid, or the uninsured, all of which warrant further research.

Conclusions

This study shows that for women with endometriosis, treatment with LA and concomitant add-back therapy was associated with better adherence to and persistence with LA over the 6 months following initiation compared with treatment with LA only. For women treated with LA along with NETA, the odds of being adherent to LA were 91% higher compared with those treated with LA only. Women treated with LA plus NETA also had 46% lower probability of discontinuing LA over 6 months. There were no significant differences in adherence and persistence between women treated with NETA versus other add-back therapies. However, NETA add-back use was

associated with lower risk of endometriosis-related surgery than other add-back therapies. Women treated with LA plus NETA had a 31% lower probability of surgery compared with women treated with LA only and a 32% lower probability of surgery compared with women treated with other therapies. The increased adherence and persistence to LA may translate into decreased need for surgical intervention. These results support increased and earlier use of NETA add-back therapy among women with endometriosis who initiate LA.

Authors

AHMED M. SOLIMAN, PhD, MS, and JANE CASTELLI-HALEY, PhD, MBA, Global Health Economics and Outcomes Research, AbbVie, North Chicago, Illinois; MACHAON BONAFEDE, PhD, MPH, and AMANDA M. FARR, MPH, Truven Health Analytics, Ann Arbor, Michigan; and CRAIG WINKEL, MD, MBA, Georgetown University School of Medicine, Washington, DC.

AUTHOR CORRESPONDENCE: Ahmed M. Soliman, PhD, MS, AbbVie, 1 N. Waukegan Rd., D-GMH 1, AP31-1, North Chicago, IL 60064. Tel.: 847.938.5475; E-mail: ahmed.m.soliman@abbvie.com.

DISCLOSURES

This study was funded by AbbVie, which also markets the endometriosis drugs Lupron and Lupaneta Pack. AbbVie participated in the study design, research, data collection, analysis and interpretation, writing, review, and approval of this publication. Soliman and Castelli-Haley are employees of AbbVie and may own AbbVie stock or stock options. Bonafede and Farr are employees of Truven Health Analytics, which received a research contract to conduct this study with and on behalf of AbbVie. Winkel is a clinical professor in the Department of Obstetrics and Gynecology at Georgetown University in Washington, DC, and has served in a consulting role on research to AbbVie for this project.

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APPENDIX A Diagnosis and Procedure Codes Used in Analysis

Code Type	Code	Description	Grouping
HCPCS	J1056	Injection, medroxyprogesterone acetate/estradiol cypionate, 5 mg/25 mg	Other add-back
HCPCS	J0900	Injection, testosterone enanthate and estradiol valerate, up to 1 cc	Other add-back
HCPCS	J0970	Injection, estradiol valerate, up to 40 mg	Other add-back
HCPCS	J1060	Injection, testosterone cypionate and estradiol cypionate, up to 1 mL	Other add-back
HCPCS	J1380	Injection, estradiol valerate, up to 10 mg	Other add-back
HCPCS	J1390	Injection, estradiol valerate, up to 20 mg	Other add-back
HCPCS	J1410	Injection, estrogen conjugated, per 25 mg	Other add-back
HCPCS	J1435	Injection, estrone, per 1 mg	Other add-back
HCPCS	J2675	Injection, progesterone, per 50 mg	Other add-back
ICD-9-CM procedure	54.11	Exploratory laparotomy	Laparotomy
ICD-9-CM procedure	54.12	Reopening of recent laparotomy site	Laparotomy
ICD-9-CM procedure	54.19	Other laparotomy	Laparotomy
ICD-9-CM procedure	54.21	Laparoscopy; peritoneoscopy	Laparoscopy
ICD-9-CM procedure	65.81	Laparoscopic lysis of adhesions of ovary and fallopian tube	Laparoscopy
ICD-9-CM procedure	65.89	Other lysis of adhesions of ovary and fallopian tube	Laparotomy
ICD-9-CM procedure	70.32	Excision or destruction of lesion of cul-de-sac	Laparotomy
ICD-9-CM procedure	57.59	Open excision or destruction of other lesion or tissue of bladder	Laparotomy
ICD-9-CM procedure	68.29	Other excision or destruction of lesion of uterus	Laparotomy
ICD-9-CM procedure	68.23	Endometrial ablation	Other excision/ablation
ICD-9-CM procedure	54.3	Excision or destruction of lesion or tissue of abdominal wall or umbilicus	Other excision/ablation
ICD-9-CM procedure	54.4	Excision or destruction of peritoneal tissue	Other excision/ablation
ICD-9-CM procedure	45.30	Endoscopic excision or destruction of lesion of duodenum	Other excision/ablation
ICD-9-CM procedure	45.31	Other local excision of lesion of duodenum	Other excision/ablation
ICD-9-CM procedure	45.32	Other destruction of lesion of duodenum	Other excision/ablation
ICD-9-CM procedure	45.33	Local excision of lesion or tissue of small intestine, except duodenum	Other excision/ablation
ICD-9-CM procedure	45.34	Other destruction of lesion of small intestine, except duodenum	Other excision/ablation
ICD-9-CM procedure	45.41	Excision of lesion or tissue of large intestine	Other excision/ablation
ICD-9-CM procedure	45.43	Endoscopic destruction of other lesion or tissue of large intestine (Note: includes both excision and destruction by endoscopic approach)	Other excision/ablation
ICD-9-CM procedure	45.49	Other destruction of lesion of large intestine (Note: open approach)	Other excision/ablation
ICD-9-CM procedure	65.25	Other laparoscopic local excision or destruction of ovary	Other excision/ablation
ICD-9-CM procedure	66.61	Excision or destruction of lesion of fallopian tube	Other excision/ablation
ICD-9-CM procedure	69.19	Other excision or destruction of uterus and supporting structures	Other excision/ablation
CPT	44200	Laparoscopy, surgical; enterolysis (separate procedure)	Laparoscopy
CPT	49321	Laparoscopy, surgical; w/bx (single/multiple)	Laparoscopy
CPT	49322	Laparoscopy, surgical, abdomen, peritoneum and omentum; w/cavity/cyst	Laparoscopy
CPT	49329	Unlisted procedure, laparoscopy, abdomen, peritoneum and omentum	Laparoscopy
CPT	56300	Deleted 01/00 lap dx (separate procedure)	Laparoscopy
CPT	56301	Deleted 01/00 lap surg; w/fulg oviducts	Laparoscopy
CPT	56302	Deleted 01/00 lap surg; w/occlud oviducts-device	Laparoscopy
CPT	56303	Deleted 01/00 lap surg; w/fulg/exc les ovary	Laparoscopy
CPT	56304	Deleted 01/00 lap surg; w/lysis adhesions	Laparoscopy
CPT	56305	Deleted 01/00 lap surg; w/bx peritoneal surface 1/mx	Laparoscopy
CPT	56306	Deleted 01/00 lap surg; w/aspirat	Laparoscopy
CPT	56309	Deleted 01/00 lap surg; w/remov leiomyomata	Laparoscopy
CPT	56310	Deleted 01/00 laparoscopy, surgical; enterolysis (freeing of intestinal adhesion)	Laparoscopy
CPT	58578	Unlisted procedure, laparoscopy, uterus	Laparoscopy
CPT	58660	Laparoscopy, surgical; w/lysis, adhesions (salpingolysis/ovariol	Laparoscopy
CPT	58661	Laparoscopy, surgical; w/removal, adnexal structures	Laparoscopy
CPT	58662	Laparoscopy, surgical; w/fulguration/excision, lesions of ovary	Laparoscopy
CPT	58670	Laparoscopy, surgical; w/fulguration of oviducts w/wo transection	Laparoscopy
CPT	58671	Laparoscopy, surgical; w/occlusion, oviducts by device	Laparoscopy
CPT	58672	Laparoscopy, surgical; w/fimbrioplasty	Laparoscopy
CPT	58673	Laparoscopy, surgical; w/salpinostomy	Laparoscopy
CPT	58679	Unlisted procedure, laparoscopy, oviduct/ovary	Laparoscopy

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APPENDIX A **Diagnosis and Procedure Codes Used in Analysis (continued)**

Code Type	Code	Description	Grouping
CPT	49320	Laparoscopy, abdomen, peritoneum and omentum; dx w/ or w/o specimen	Laparoscopy
CPT	49000	Explor laparotomy w/wo bx (separate procedure)	Laparotomy
CPT	49002	Reopening of recent laparotomy	Laparotomy
CPT	49010	Explor retroperitoneal (separate procedure)	Laparotomy
CPT	49200	Exc intra-abd/retroperitoneal tumor	Laparotomy
CPT	49201	Exc intra-abd tumors/cysts; exten	Laparotomy
CPT	58740	Lysis adhesions	Laparotomy
CPT	58805	Drain ovarian cyst (separate procedure); ABD	Laparotomy
CPT	58925	Ovarian cystectomy unilat/bilat	Laparotomy
CPT	58563	Hysteroscopy, surgical; w/endometrial ablation	Other excision/ablation
CPT	56356	Deleted 01/00 hysteroscopy surg; w/endometr ablation	Other excision/ablation
CPT	58353	Ablation, endometrial, thermal, w/o hysteroscopic guidance	Other excision/ablation
CPT	58356	Endometrial cryoablation with ultrasonic guidance, including endometrial curettage, when performed	Other excision/ablation
ICD-9-CM procedure	68.3	Subtotal abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.31	Laparoscopic supracervical hysterectomy (LSH)	Hysterectomy
ICD-9-CM procedure	68.39	Other and unspecified subtotal abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.4	Total abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.41	Laparoscopic total abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.49	Other and unspecified total abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.5	Vaginal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.51	Laparoscopically assisted vaginal hysterectomy (LAVH)	Hysterectomy
ICD-9-CM procedure	68.59	Other and unspecified vaginal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.6	Radical abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.61	Laparoscopic radical abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.69	Other and unspecified radical abdominal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.7	Radical vaginal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.71	Laparoscopic radical vaginal hysterectomy (LVRH)	Hysterectomy
ICD-9-CM procedure	68.79	Other and unspecified radical vaginal hysterectomy	Hysterectomy
ICD-9-CM procedure	68.8	Pelvic evisceration	Used to exclude patients only
ICD-9-CM procedure	68.9	Other and unspecified hysterectomy	Hysterectomy
CPT	51925	Closure of vesicouterine fistula; with hysterectomy	Hysterectomy
CPT	56308	Deleted 01/00 lap surg; w/vag hyst w/wo tube(s)	Hysterectomy
CPT	58150	TAH w/wo remov tube(s) - ovary(s)	Hysterectomy
CPT	58152	TAH; w/colpo-urethrocystopexy	Hysterectomy
CPT	58180	Supracerv ABD hyst w/wo remov tube	Hysterectomy
CPT	58200	TAH w/part vaginect w/lymph node	Hysterectomy
CPT	58210	Rad ABD hyst w/tot pelvic lymphaden	Used to exclude patients only
CPT	58240	Pelvic exenteration-gyn malig w/TAH	Used to exclude patients only
CPT	58260	Vag hyst	Hysterectomy
CPT	58262	Vag hyst; w/remov tube and/or ovary	Hysterectomy
CPT	58263	Vag hyst; tube/ovary w/repr enteroc	Hysterectomy
CPT	58267	Vag hyst; w/colpo-urethrocystopexy	Hysterectomy
CPT	58270	Vag hyst; w/repr enterocele	Hysterectomy
CPT	58275	Vag hyst w/tot/part colpectomy	Hysterectomy
CPT	58280	Vag hyst w/colpect; w/repr enteroce	Hysterectomy
CPT	58285	Vag hyst radical	Hysterectomy
CPT	58290	Vaginal hysterectomy, for uterus greater than 250 g	Hysterectomy
CPT	58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58292	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s), with repair of enterocele	Hysterectomy
CPT	58293	Vaginal hysterectomy, for uterus greater than 250 g; with colpo-urethrocystopexy (Marshall-Marchetti-Krantz type, pereyra type) with or without endoscopic control	Hysterectomy
CPT	58294	Vaginal hysterectomy, for uterus greater than 250 g; with repair of enterocele	Hysterectomy

**Analysis of Adherence, Persistence, and Surgery Among Endometriosis Patients
Treated with Leuprolide Acetate Plus Norethindrone Acetate Add-Back Therapy**

APPENDIX A Diagnosis and Procedure Codes Used in Analysis (continued)

Code Type	Code	Description	Grouping
CPT	58541	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less	Hysterectomy
CPT	58542	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58543	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g	Hysterectomy
CPT	58544	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58548	Laparoscopy, surgical, with radical hysterectomy, with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy), with removal of tube(s) and ovary(s), if performed	Hysterectomy
CPT	58550	Laparoscopy, surgical; w/ vaginal hysterectomy w/wo removal ovary	Hysterectomy
CPT	58552	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58553	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g	Hysterectomy
CPT	58554	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58570	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less	Hysterectomy
CPT	58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	58572	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g	Hysterectomy
CPT	58573	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	Hysterectomy
CPT	59135	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy	Hysterectomy
CPT	59136	Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus	Hysterectomy
CPT	52078	Laparoscopic supracervical hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)	Hysterectomy
CPT	58953	Bilat salpingo-oophorect w/omentec, total abdom	Hysterectomy
CPT	58954	Bilat salping-oophorec w/omentec, tl abdom hyst & lymphadenectomy	Hysterectomy
CPT	58956	Bilateral salpingo-oophorectomy with total omentectomy, total abdominal hysterectomy for malignancy	Hysterectomy
ICD-9-CM procedure	65.3	Unilateral oophorectomy	Oophorectomy
ICD-9-CM procedure	65.31	Laparoscopic unilateral oophorectomy	Oophorectomy
ICD-9-CM procedure	65.39	Other unilateral oophorectomy	Oophorectomy
ICD-9-CM procedure	65.4	Unilateral salpingo-oophorectomy	Oophorectomy
ICD-9-CM procedure	65.41	Laparoscopic unilateral salpingo-oophorectomy	Oophorectomy
ICD-9-CM procedure	65.49	Other unilateral salpingo-oophorectomy	Oophorectomy
ICD-9-CM procedure	65.5	Bilateral oophorectomy	Oophorectomy
ICD-9-CM procedure	65.51	Other removal of both ovaries at same operative episode	Oophorectomy
ICD-9-CM procedure	65.52	Other removal of remaining ovary	Oophorectomy
ICD-9-CM procedure	65.53	Laparoscopic removal of both ovaries at same operative episode	Oophorectomy
ICD-9-CM procedure	65.54	Laparoscopic removal of remaining ovary	Oophorectomy
ICD-9-CM procedure	65.6	Bilateral salpingo-oophorectomy	Oophorectomy
ICD-9-CM procedure	65.61	Other removal of both ovaries and tubes at same operative episode	Oophorectomy
ICD-9-CM procedure	65.62	Other removal of remaining ovary and tube	Oophorectomy
ICD-9-CM procedure	65.63	Laparoscopic removal of both ovaries and tubes at same operative episode	Oophorectomy
ICD-9-CM procedure	65.64	Laparoscopic removal of remaining ovary and tube	Oophorectomy
CPT	58940	Oophorectomy part/tot unilat/bilat	Oophorectomy
CPT	58943	Oophorectomy; ovarian malig w/bx	Oophorectomy

CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B List of Add-Back Therapy Medications

NETA Add-Back Therapies	Other Add-Back Therapies
Norethindrone acetate	Conjugated estrogens
	Conjugated estrogens/medroxyprogesterone acetate
	Conjugated estrogens/meprobamate
	Desogestrel/ethinyl estradiol
	Drospirenone/estradiol
	Drospirenone/ethinyl estradiol/levomefolate calcium
	Esterified estrogens
	Esterified estrogens/methyltestosterone
	Estradiol
	Estradiol acetate
	Estradiol cypionate
	Estradiol cypionate/medroxyprogesterone acetate
	Estradiol valerate
	Estradiol valerate/dienogest
	Estrone
	Estropipate
	Ethinyl estradiol/drospirenon
	Ethinodiol diacetate/ethinyl estradiol
	Etonogestrel/ethinyl estradiol
	Levonorgestrel
	Levonorgestrel/ethinyl estradiol
	Medroxyprogesterone acetate
	Medroxyprogesterone acetate/estradiol cypionate
	Micronized progesterone
	Norelgestromin/ethinyl estradiol
	Norethindrone
	Norethindrone acetate/ethinyl estradiol
	Norethindrone acetate/ethinyl estradiol/ferrous fumarate
	Norethindrone/ethinyl estradiol
	Norethindrone/ethinyl estradiol/ferrous fumarate
	Norethindrone/mestranol
	Norgestimate/ethinyl estradiol
	Norgestrel
	Norgestrel/ethinyl estradiol
	Progesterone
	Testosterone cypionate/estradiol cypionate
	Testosterone enanthate/estradiol valerate