Medical Cost and Healthcare Resource Utilization Reductions for Zuranolone Relative to SSRIs in the Treatment of Postpartum Depression

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Background

- Postpartum depression (PPD) is:
  - One of the most common perinatal conditions, with roughly 1 in 8 women reporting symptoms after a recent live birth in 2018.[1]
  - Defined as onset of a major depressive episode during pregnancy or within the first 4 weeks to 12 months following childbirth, based on varying definitions from different professional organizations.[1-5]
  - Different from the "baby blues," which typically peaks within the first week postpartum, resolves without treatment within 2 weeks, has a different symptom profile, and does not impact the mother's ability to care for herself or her family.[6]
- In the United States (US), the direct medical costs and healthcare resource utilization (HCRU) burden associated with PPD is substantial.
  - Research has found that in 2009-2016 in the US, mothers affected by PPD incurred 27% greater all-cause insurer healthcare costs compared with mothers without PPD ($19,611 vs. $15,410).[7]
  - The same study found that households affected by PPD spent $13,601 more (22% increase) on medical and pharmaceutical costs than households not affected by PPD in the first year after childbirth alone.[7]
- Although selective serotonin reuptake inhibitors (SSRIs) are commonly used in clinical practice for PPD treatment,[8] they are not approved by the US Food and Drug Administration (FDA) for use in PPD[8] and may require 6 to 12 weeks to demonstrate maximum efficacy in some patients.[9]
- Zuranolone is approved by the FDA as an oral, once-daily, 14-day treatment course indicated for adults with PPD in the US. In the placebo-controlled, phase 3 SKYLARK clinical trial of zuranolone (NCT04442503), patients treated with zuranolone demonstrated a statistically significant improvement in depressive symptoms versus placebo, as assessed by change from baseline in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score, at day 15 (primary endpoint) and as early as day 3 (key secondary endpoint).[10]
- This analysis builds on the findings of a previous cost-effectiveness analysis of zuranolone[11] by focusing on the nonpharmacy direct medical costs in the year immediately postpartum, when patients incur the greatest HCRU related to PPD.[11]

Objective

- To estimate direct nonpharmacy medical costs and HCRU associated with zuranolone use relative to SSRIs in the treatment of adults with PPD.

Methods

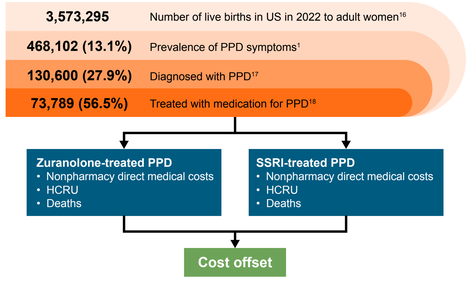
Model Structure

- A cost offset analysis was developed to estimate nonpharmacy costs for PPD treatment with zuranolone or a basket of SSRIs, as they are the most commonly prescribed class in PPD.
  - SSRIs included paroxetine, fluoxetine, and the basket of SSRIs studied in Sharp et al.[12]
  - Dosing for zuranolone was a 14-day course of 50 mg orally once per day.[13]
- A payer perspective and a 1-year time horizon were used.
- The Excel-based model calculates the estimated size of the number of adults diagnosed with and treated for PPD in the US in 2022.
- Nonpharmacy costs are calculated for this cohort assuming that they were either 100% treated with zuranolone or 100% treated with an SSRI; the difference in costs (i.e., cost offset) is then calculated **(Figure 1)**.
- Treatment switching and discontinuation are not modeled.

Population

- The modeled population was the incident cohort of all US women (aged ≥ 18 years) who delivered live births in 2022, who experienced PPD symptoms, and who would have been diagnosed with and pharmacologically treated for PPD **(Figure 1)**.
- The age-adjusted, gender-specific, general US population mortality from 2020 was used[14] and adjusted for the excess risk of death among women with PPD versus the general population using a relative risk of 1.75.[15] The modeled population was assumed to be 100% adult females.
- To calculate age-adjusted mortality, the women in the cohort were assumed to be aged 30 years at the start of modeling, in line with the average age at baseline in the key zuranolone clinical trial.[10]

FIGURE 1. MODEL STRUCTURE



Costs

- PPD-related HCRU (inpatient admissions and visits to healthcare providers, specialists for diagnosis and treatment, and emergency departments [ED]) were estimated, as well as associated nonpharmacy direct medical costs, including costs for screening, diagnosis, and treatment-related adverse events (AEs) **(Table 1 and Table 2)**.
- Costs were adjusted to 2023 US dollars (USD)[19] where necessary and were not discounted.
- Drug acquisition costs and other pharmacy costs, including pharmacy costs relating to AEs, were not considered.
- We assumed that healthcare visits were equally distributed throughout the year, regardless of treatment.
- Treatment location was based on the HCRU patterns observed in the cited literature.
- Women were assumed to accrue no PPD-related HCRU or associated costs if they were no longer exhibiting symptoms of PPD.

TABLE 1. HCRU FOR PATIENTS EXPERIENCING PPD SYMPTOMS

RESOURCE USE	Annual value	Source
Screening and diagnosis costs applicable to all diagnosed patients		
Screening	1 GP/OBGYN visit	Assumption that screening is performed in an GP/OBGYN visit and that half of women are diagnosed in the same visit with their GP/OBGYN and half are subsequently diagnosed through referral to a psychiatrist
Diagnosis	0.5 psychiatric diagnosis visits	
Annual HCRU for patients experiencing PPD symptoms and being treated		
GP/OBGYN visits	8	Epperson et al.[7]
Psychiatrist visits	3	Sherman and Ali[18]
ED visits	0.27	Dagher et al.[20]
Inpatient days	1	Epperson et al.[7]
HCRU use per treatment-related adverse event[a]		
AE event (excepting libido decrease)	1 GP/OBGYN visit	Sullivan et al.[21]
Libido decrease AE event	2 GP/OBGYN visits	

GP = general practitioner; OBGYN = obstetrician or gynecologist.
[a] The number of GP visits per AE event is assumed to apply regardless of the duration of treatment.

TABLE 2. COST INPUTS FOR HCRU ASSOCIATED WITH PPD TREATMENT, 2023 US $

HCRU COSTS	Value	Source
Cost per GP/OBGYN visit	$56.93	CPT 99212[22]
Cost per psychiatric diagnosis visit	$196.55	CPT 90792[22]
Cost per psychiatric treatment visit	$99.97	CPT 90834[22]
Cost per ED visit	$576.94	HCUP data for ED visits for depressive episodes from 2017 inflated to 2023 USD[23]
Cost per inpatient day (acute psychiatric ward)	$1,052.16	Weighted national estimates from HCUP National (Nationwide) Inpatient Sample, 2000-2020[24]; inflated to 2023 USD from 2020 USD[19]

CPT = Current Procedural Terminology; HCUP = Healthcare Cost and Utilization Project.

Clinical Effectiveness

- Clinical effectiveness inputs were sourced from an indirect treatment comparison conducted using SKYLARK trial data.[13]
  - In general, indirect treatment comparisons are conducted when head-to-head clinical trial data comparing treatments are unavailable.
- It was assumed that changes in Edinburgh Postnatal Depression Scale (EPDS) score over time applied equally to patients with PPD with moderate or severe symptoms.
- It was also assumed that the baseline EPDS distribution matched what was observed in the SKYLARK trial, with a mean EPDS score of 21.1 (standard deviation, 3.7).[13] This corresponded to 19% being in EPDS states 14-18 and the remaining 81% in EPDS states 19-30, assuming a normal distribution and all individuals starting in an EPDS state corresponding to depression.
- PPD severity was adjusted at baseline in the indirect treatment comparison, and after matching, disease severity was similar between the placebo- and zuranolone-treated groups.

TABLE 3. CLINICAL EFFECTIVENESS INPUTS

	Change from baseline EPDS		Source
Observation day	**Zuranolone**	**SSRIs[a]**	
Day 3	-2.87	-1.96	Meltzer-Brody et al.[13]
Day 15	-7.02	-2.50	
Day 28	-8.33	-3.33	
Day 45	-9.85	-2.69	
LOCF[b]	-9.85	-5.75	

LOCF = last observation carried forward. [a] SSRIs included paroxetine, fluoxetine, and the basket of SSRIs studied in Sharp et al.[12]
[b] Last observation occurred at day 45 for zuranolone and weeks 12-18 for SSRIs.

AEs

- AEs from sertraline were used to represent AEs for SSRIs as a class, as sertraline is commonly used[25] and shares many of the most common AEs that are observed across SSRIs as a class.[25,26]
- For inclusion, AEs had to have greater than 5% incidence and twice the incidence in the treatment (either zuranolone or SSRIs) group as in the placebo group from each respective prescribing information[27,28] **(Table 4)**. Any AE meeting these criteria for either zuranolone or sertraline was included, even if the incidence did not meet these criteria for the other treatment. In these cases, the relative increase in incidence versus the placebo group was used.
- AE costs for zuranolone are calculated based on trial data with 45 days of follow-up and applied for 14 days to reflect the recommended duration of treatment.[28] AE costs for SSRIs are applied for a full year, in line with the recommendation to continue treatment for 6 to 9 months after remission is achieved,[29] which typically occurs in 6 to 12 weeks if the first treatment is successful.[9]

TABLE 4. INCIDENCE OF AES

ADVERSE EVENT	Zuranolone	SSRIs	Source
Fatigue	5%	6%	AEs for zuranolone based on 14 days of exposure and 45 days of follow-up.[28] AEs for SSRIs based on 8-12 weeks of exposure.[27]
Nausea	12%[a]	26%	
Diarrhea	14%	20%	
Dyspepsia	4%[a]	8%	
Decreased appetite	2%[a]	7%	
Tremor	2%	9%	
Somnolence	36%	11%	
Libido decrease	2%[a]	6%	
Hyperhidrosis	3%[a]	7%	

[a] Zuranolone assumed equivalent to untreated group in sertaline prescribing information for this AE because it was not reported in the prescribing information for zuranolone.

Outcomes

- Outcomes included total and per-treated-person direct medical costs in 2023 US dollars and total HCRU.
- Nonpharmacy direct costs included outpatient costs, inpatient costs, AE costs, and ED costs.
- HCRU outcomes included outpatient visits, inpatient days, AE-related visits, and ED visits.

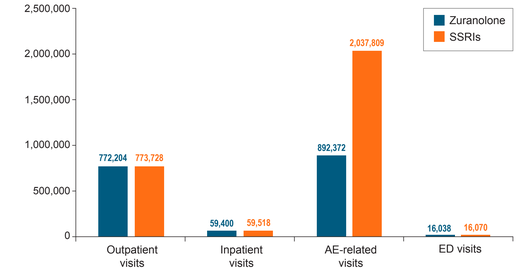
Results

- From an adult US population perspective, 3,573,295 women aged ≥18 years had a live birth in 2022, of whom an estimated 13.1% experienced PPD symptoms (n = 468,102). Among those experiencing symptoms, an estimated 27.9% (n = 130,600) were diagnosed with PPD, and an estimated 56.6% of diagnosed patients were pharmacologically treated (n = 73,789) **(Figure 1)**.

HCRU

- Compared with SSRIs, zuranolone treatment was associated with reduced HCRU across all modeled categories: 1,524 fewer outpatient visits; 117 fewer inpatient days; 1,145,437 fewer AE-related visits; and 32 fewer ED visits over the 12-month period.

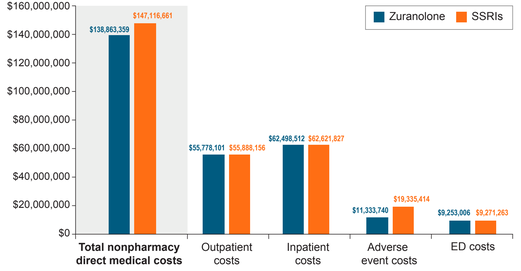
FIGURE 2. MODELED 1-YEAR HCRU FOR US ADULT PPD PATIENTS



Costs

- Among the modeled cohort of adults diagnosed with PPD and pharmacologically treated (n = 73,789), zuranolone use was associated with $138.9 million in direct medical costs over 1 year compared with $147.1 million associated with SSRI use. This reduction in HCRU was linked with a corresponding decrease in nonpharmacy direct medical costs of $8.3 million annually.
- Overall, nonpharmacy direct medical costs per treated adult were estimated to be $1,882 with zuranolone and $1,994 with SSRIs per year. Correspondingly, per treated adult, treatment with zuranolone was associated with a decrease of $112 per year in nonpharmacy direct medical costs compared with treatment with SSRIs.
- The calculated average annual cost of AEs per treated patient for zuranolone was $153.60 and for SSRIs was $262.04.

FIGURE 3. MODELED 1-YEAR DIRECT NONPHARMACY MEDICAL COSTS FOR US ADULT PPD PATIENTS



Limitations

- Limitations of this study include the following:
  - Direct head-to-head clinical effectiveness data for zuranolone and SSRIs was not available, although this limitation was mitigated by use of an indirect treatment comparison analysis.[13]
  - The model used a short, 1-year time horizon, which was selected to correspond to the clinical trial data available for zuranolone and to reflect a 1-year formulary planning calendar.
  - Cost and HCRU values may underestimate actual household spending due to PPD, as only the mother's contribution to cost and HCRU is considered.
  - Data underlying the model from clinical trials may not be representative of a real-world PPD patient population, including severity, comorbidities, and prior psychiatric history. The results may not be generalizable to a patient population experiencing mild depression, having comorbidities, or having a prior history of psychiatric conditions or treatment.
  - Data used in the model to estimate PPD-related costs and HCRU were derived from the published literature due to the lack of long-term HCRU data associated with zuranolone treatment. These data may not reflect the true costs and HCRU associated with zuranolone use.

Conclusions

- Compared with SSRIs, our 1-year model estimated that treatment with zuranolone may result in offsets for nonpharmacy direct medical costs and HCRU for adults with PPD.
- In this model-based analysis, the majority of the reduction in nonpharmacy direct medical costs was attributable to AE-related costs.

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