CME Journal of Neurology and Neuroscience Research Article

Cost-Effectiveness of Medically Monitored Ibogaine for Opioid Use Disorder in Tennessee: A State-Specific Semi-Markov Analysis

T Wagner[1], Gaetano Lardieri[2]*, and KD Adams[3]

[1]Research Fellow at the Perelman School of Medicine at the University of Pennsylvania, Pennsylvania, USA.

[2]Advisory Board Member for the Coalition for Medical Marijuana and Special Executive Advisor for CannaCoverage LLC., USA.

[3]Owner of LYT Marketing and Media LLC., USA.

Correspondence

Gaetano Lardieri, Advisory Board Member for the Coalition for Medical Marijuana and Special Executive Advisor for CannaCoverage LLC., USA.

Received Date: 13 April 2026

Revised Date: 21 May 2026

Accepted Date: 30 May 2026

Publication Date: 08 June 2026

Abstract

Background: Opioid use disorder remains a major public health and healthcare-system challenge in Tennessee, where many adults remain untreated, undertreated, or poorly retained in care. Medically monitored ibogaine has been proposed as a potential intervention for OUD, but its economic implications in a state treatment environment have not been well characterized. We evaluated the health and economic consequences of adding a medically monitored ibogaine pathway to heterogeneous standard care for Tennessee adults with OUD.

Methods: We developed a Tennessee-specific cohort state-transition model with semi-Markov features comparing realistic limited-access medically monitored ibogaine with a matched no-ibogaine standard-care reference. The modeled comparator included methadone, buprenorphine, extended-release naltrexone, non-MOUD treatment, and untreated or not-engaged care. The base-case cohort represented 106,000 Tennessee adults with OUD. The model used weekly cycles, a 10-year horizon, 3% annual discounting, and a healthcare-sector perspective. The primary cost endpoint was cumulative direct medical cost; primary health outcomes were quality-adjusted life-years, survival, and mortality. Scenario analyses, one-way deterministic sensitivity analysis, probabilistic sensitivity analysis with 5000 simulations, and program-cost threshold analysis were conducted.

Results: In the 10-year base case, medically monitored ibogaine was associated with lower direct medical cost, higher QALYs, and improved survival. Cumulative direct medical cost was $5.46 billion with ibogaine versus $6.42 billion with no ibogaine, yielding an incremental direct-cost difference of -$965.0 million. Total QALYs were 627,371 versus 530,144, corresponding to an incremental gain of 97,227 QALYs. Ten-year survival was 0.9308 versus 0.9098, an absolute survival gain of 2.10 percentage points. Because ibogaine was less costly and more effective in the base case, it was dominant. In scenario analyses, ibogaine remained less costly and more effective under waning efficacy and comparator-mix variation. In the conservative stress test, direct medical cost increased by $232.7 million, but ibogaine still produced 68,547 additional QALYs. In probabilistic sensitivity analysis, 72.9% of simulations were direct-medical-cost-saving, and 99.98%, 100%, and 100% were cost-effective at willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY, respectively. Program-cost threshold analysis showed that ibogaine remained approximately cost-saving at $11,000 per treatment episode but became more costly at $15,000.

Conclusions: In this Tennessee-specific decision-analytic model, adding a medically monitored ibogaine pathway to heterogeneous standard care was associated with lower direct medical cost, higher QALYs, and improved survival over 10 years. Cost savings were sensitive to program cost and durability assumptions, but health gains persisted across conservative scenarios. These findings do not establish ibogaine as routine OUD care, but they suggest that a carefully monitored Tennessee ibogaine clinical-trial or implementation pathway could be economically plausible if it reduces relapse, hospitalization, and mortality while maintaining appropriate cardiac safety monitoring and escalation capacity.

Keywords

Opioid Use Disorder (OUD), Ibogaine, Cost-Effectiveness Analysis, Economic Evaluation, Decision-Analytic Modeling, State-Transition Model, Quality-Adjusted Life Years (QALYs), Medication for Opioid Use Disorder (MOUD).

INTRODUCTION

Opioid use disorder (OUD) remains a major cause of preventable morbidity, mortality, and healthcare utilization in the United States, despite the availability of effective medications and established treatment pathways. National data continue to show a substantial gap between the number of adults with OUD and the number receiving medication treatment, leaving many patients untreated, undertreated, or engaged in care that does not include medications for OUD [1,2]. This treatment gap has clinical and economic consequences. Medication-based treatment pathways, particularly opioid agonist treatment, are associated with lower overdose risk, reduced acute-care utilization, and lower mortality compared with untreated or recently discontinued care [3-5].

Tennessee is a particularly relevant setting in which to examine this problem. The 2023–2024 National Survey on Drug Use and Health state estimates indicate that approximately 106,000 Tennessee adults had past-year OUD, and the state continues to experience a substantial overdose burden [6,7]. Tennessee overdose-related hospital-discharge data further underscore the continuing acute-care burden associated with drug overdose, including inpatient and outpatient encounters that reflect the health-system consequences of unstable substance-use trajectories [8]. At the same time, Tennessee has developed a buprenorphine-oriented treatment infrastructure through TennCare's BESMART network and related office-based treatment efforts [9,10]. The result is not an absence of OUD treatment infrastructure, but a heterogeneous treatment environment in which access, retention, medication pathway mix, and disengagement remain central policy concerns.

Economic evaluation is useful in this context because the relevant policy question is not only whether effective OUD treatments exist, but whether the treatment system can reduce downstream hospitalization, relapse, disengagement, and mortality at an acceptable cost. Prior OUD economic models have shown that treatment value is strongly shaped by retention, overdose protection, treatment access, and the balance between up-front treatment costs and downstream acute-care offsets [11,12]. These studies provide an important benchmark for evaluating new treatment pathways, but they do not directly answer how a medically monitored ibogaine pathway would perform in a state-specific treatment environment.

Ibogaine has attracted renewed interest as a potential intervention for OUD because observational studies suggest that supervised administration may reduce withdrawal severity, support early transition out of opioid dependence, and produce short-term abstinence or remission in some patients [13-15]. However, the evidence base remains limited, nonrandomized, and protocol-sensitive. Systematic reviews have emphasized both the potential clinical signal and the need for caution given heterogeneity in study designs, limited long-term comparative evidence, and unresolved safety concerns [16,17].

The safety issue is not incidental. Ibogaine has been associated with QTc prolongation and clinically important cardiac risk during administration, and mechanistic evidence implicates hERG channel inhibition as one plausible contributor to proarrhythmic liability [18,19]. These concerns define the intervention that can be responsibly evaluated. A policy-relevant ibogaine pathway is not an unmonitored detoxification episode; it requires screening, medically supervised administration, cardiac monitoring, safety-escalation capacity, and post-acute follow-up. The economic question is therefore whether a resource-intensive monitored pathway could still be clinically and economically attractive after accounting for the infrastructure required for safe implementation.

That question has become more immediate as Tennessee and federal policymakers consider structured pathways for psychedelic and ibogaine-related research. Tennessee's HOPE Treatment Act creates a state-level framework for ibogaine drug-development clinical trials, while recent federal policy has signaled interest in pathways for investigational psychedelic therapies, including ibogaine compounds [20,21]. These policy developments do not establish clinical effectiveness or cost-effectiveness. They do, however, make explicit the need for decision-analytic evidence that can inform trial design, implementation planning, coverage discussions, and state-level resource allocation.

To our knowledge, no Tennessee-specific decision-analytic study has evaluated the long-term healthcare-sector implications of adding medically monitored ibogaine to the state's heterogeneous OUD treatment environment. We therefore developed a Tennessee-focused semi-Markov cohort model comparing realistic limited-access medically monitored ibogaine with a matched no-ibogaine standard-care reference. The comparator included methadone, buprenorphine, extended-release naltrexone, non-MOUD treatment, and untreated or not-engaged care. The base-case analysis used a 10-year healthcare-sector perspective, with direct medical cost as the primary cost endpoint and QALYs and survival as primary health outcomes. We hypothesized that any modeled value of ibogaine would arise primarily through longer-term changes in relapse, hospitalization, treatment disengagement, stable recovery, and mortality rather than through short-term detoxification effects alone.

METHODS

Study design and analytic objective

We developed a cohort state-transition model with semi-Markov features to estimate the health and economic consequences of adding a medically monitored ibogaine pathway to Tennessee's existing opioid use disorder treatment environment. The analysis compared a realistic limited-access ibogaine strategy with a matched no-ibogaine reference reflecting heterogeneous standard care. The model was structured as a state-specific policy analysis rather than as a treatment-engaged clinical trial simulation. The target estimand was the incremental 10-year effect of permitting eligible Tennessee adults with OUD to enter a medically monitored ibogaine pathway while preserving the same standard-care pathways available in the reference arm.

The base-case analysis adopted a healthcare-sector perspective and treated cumulative direct medical cost as the primary cost endpoint. Primary health outcomes were quality-adjusted life-years, survival probability, and mortality probability. Blended total cost, which included indirect costs, was tracked as a secondary outcome rather than as the primary healthcare-sector endpoint. The analysis was designed and reported in alignment with CHEERS 2022 principles for transparent model-based economic evaluation [22].

Target population

The modeled cohort represented Tennessee adults with past-year OUD. The base-case cohort size was 106,000 adults, corresponding to the 2023–2024 NSDUH Tennessee adult OUD estimate used in the finalized Tennessee overlay [6]. To avoid overdependence on a single denominator estimate, the model also included denominator sensitivity scenarios representing the lower and upper credible-interval bounds from the 2023–2024 NSDUH estimate, as well as a historical 2022–2023 Tennessee denominator scenario. Tennessee

overdose mortality and overdose-related hospital-discharge data were used as state-context and benchmark inputs rather than as direct substitutes for transition probabilities unless an explicit conversion was specified [7,8].

Intervention and comparator

The intervention was medically monitored ibogaine embedded within an OUD care pathway. The modeled intervention included protocolized administration, cardiac screening and monitoring, safety-escalation capacity, post-acute stabilization, and follow-up. It was not intended to represent unmonitored, minimally supervised, or low-resource ibogaine use. This distinction was central because the clinical literature identifies cardiac safety, including QTc prolongation and monitoring-intensive adverse events, as a key implementation constraint for ibogaine administration [16-18]. Mechanistic evidence that ibogaine inhibits hERG channels further supports treating cardiac monitoring as part of the intervention definition rather than as an optional implementation detail [19].

The comparator was a heterogeneous no-ibogaine standard-care basket rather than a single optimized treatment arm. It included methadone, buprenorphine, extended-release naltrexone, non-medication treatment, and untreated or not-engaged care. This comparator was selected because the decision problem concerns the addition of a new monitored pathway to Tennessee's existing treatment environment, not a head-to-head trial against idealized buprenorphine retention among already-engaged patients. The comparator structure was informed by national OUD treatment-access data, comparative pathway evidence, and OUD economic modeling literature [1,3,11,12].

The Tennessee overlay used a baseline routing mix of 5.0% methadone, 22.0% buprenorphine, 1.5% extended-release naltrexone, 23.5% non-MOUD treatment, and 48.0% untreated or not engaged. These shares were treated as Tennessee-specific overlay assumptions rather than definitive all-payer empirical estimates. The buprenorphine-heavy and methadone-constrained structure reflected Tennessee's office-based buprenorphine infrastructure and the continued relevance of untreated or poorly engaged care [9,10]. Both the ibogaine-enabled and no-ibogaine arms began from the same baseline routing structure. The ibogaine-enabled arm differed only by allowing eligible transitions from selected clinical states into medically monitored ibogaine.

Model structure

The model used weekly cycles over a 10-year base-case horizon. Costs and QALYs were discounted at 3% annually. The model contained 15 health states and 36 transitions, with state-conditioned costs, transition-conditioned event costs, state utilities, and state-specific mortality rules. Death was modeled as an absorbing state.

A semi-Markov structure was used because several clinically important phases of OUD care are time-dependent, including treatment induction, post-discontinuation risk, monitored ibogaine administration, safety escalation, post-acute stabilization, early remission, hospitalization, and relapse after recovery. Tunnel states and time-in-state logic allowed costs, utilities, and transition risks to vary by clinical phase rather than assuming constant risk over all time spent in a state. This structure follows good-practice recommendations for state-transition models in which clinically meaningful history, timing, or duration effects cannot be represented adequately by a simple memoryless Markov process [23].

The standard-care structure included heterogeneous routing into methadone, buprenorphine, extended-release naltrexone, non-MOUD treatment, untreated active use, recent dropout or tolerance-loss risk, hospitalization or acute-care events, stable recovery, and death. The ibogaine-enabled structure added monitored ibogaine administration, safety escalation, post-acute stabilization, early ibogaine remission, and subsequent stable recovery, relapse, or re-engagement pathways. Treatment discontinuation and periods out of care were modeled explicitly because mortality risk is higher after discontinuation of opioid agonist treatment and after non-medication or unsupported treatment episodes [3-5].

Mortality and competing risks

The model incorporated background mortality and state-specific excess mortality. Mortality risk varied across in-treatment states, out-of-treatment states, recent dropout or tolerance-loss states, hospitalization, and monitored ibogaine-related states. Medication treatment and treatment retention were modeled as protective relative to untreated or recently discontinued care, consistent with observational and meta-analytic OUD evidence [3-5].

Mortality was handled as a competing event within each cycle. For each source state, the engine computed mortality and nonfatal transition probabilities within a single cycle-level probability framework rather than layering death independently on top of nonfatal transitions. This approach preserved feasible transition probabilities and maintained death as a competing event rather than an additional event superimposed on other transitions [23].

Representation of ibogaine safety and cardiac toxicity

Ibogaine safety was represented structurally rather than as an incidental adverse-event adjustment. Patients entering the ibogaine pathway passed through monitored administration and could enter a safety-escalation state before post-acute stabilization, early remission, relapse, or return to active use. The safety-escalation structure captured the fact that medically plausible ibogaine delivery requires clinical monitoring and escalation capacity, particularly given cardiac safety concerns reported in the ibogaine literature [16-19].

The model included costs for ibogaine program delivery, monitored care, safety escalation, and early aftercare. These costs were treated as implementation-sensitive and localizable. The safety calibration framework included return to opioid use within 24 hours after ibogaine and QTc greater than 500 ms during monitored administration. These targets should be interpreted as protocol-sensitive safety anchors rather than universal adverse-event rates. The analysis therefore evaluates medically monitored ibogaine, not unsupervised ibogaine exposure.

Costs and utilities

Costs were assigned through state-conditioned and transition-conditioned rules. Standard-care costs included methadone treatment, buprenorphine management, extended-release naltrexone administration, non-MOUD treatment, hospitalization or overdose-related acute care, and other pathway-specific costs. Ibogaine-specific costs included program delivery, monitored care, safety escalation, and post-acute follow-up. All cost rules with source-year metadata were inflated to 2024 U.S. medical-care dollars before deterministic, scenario, DSA, PSA, or threshold analyses.

Because several Tennessee-specific cost inputs remain difficult to

observe from public data, local treatment, hospitalization, monitoring, and ibogaine program costs were retained as publication-sensitive parameters. They were included in deterministic sensitivity analysis, probabilistic sensitivity analysis, or threshold analysis when relevant. Prior OUD cost-effectiveness studies and national burden estimates informed the general economic framing and cost categories [11,12,24].

Utilities were assigned at the state level and accumulated over time as QALYs. Utility inputs reflected health-related quality of life in active OUD, treatment engagement, withdrawal-related or unstable states, remission, and recovery. Utility anchors were informed by OUD quality-of-life studies and prior economic evaluations [11,25-27].

Parameterization and uncertainty

Model inputs were drawn from a structured evidence and provenance registry. Each transition, cost, utility, mortality, and routing parameter carried a base value, uncertainty metadata, citation references where available, and a source classification. Parameters were classified as literature-based, calibrated, registry-derived, localizable, expert-assumption, or overlay-specific. This distinction was retained in the exported parameter and provenance tables.

The finalized Tennessee overlay included 24 uncertainty-registry entries. Probabilities and utilities were assigned bounded distributions where appropriate, cost parameters were assigned nonnegative or right-skewed distributions when warranted, and localizable parameters were assigned ranges intended to reflect plausible implementation uncertainty. Where direct variance estimates were unavailable, uncertainty bounds were specified transparently and evaluated through deterministic and probabilistic sensitivity analysis. Comparator pathway shares, ibogaine program cost, monitored-care cost, safety-escalation probability and cost, long-run durability, and selected mortality parameters were treated as high-priority uncertainty domains. This approach follows good-practice recommendations that model-based economic evaluations should distinguish parameter estimation, uncertainty characterization, and sensitivity analysis rather than treating uncertainty as a post hoc robustness exercise [28].

Scenario analyses

Scenario analyses evaluated structural and policy uncertainty that could not be represented adequately by one-parameter variation alone. The prespecified scenario set included the realistic publication base case, waning efficacy, comparator-mix variation, a conservative publication stress test, retreatment or re-engagement, short horizon, and denominator sensitivity scenarios. The waning-efficacy scenario increased relapse after ibogaine remission. The comparator-mix scenario tested sensitivity to the Tennessee routing structure. The conservative stress test combined less favorable ibogaine response, faster relapse, stronger comparator performance, and higher monitored-care cost. The short-horizon scenario examined whether value was visible over the immediate post-administration period rather than over the full 10-year horizon.

Scenario analyses were kept separate from probabilistic sensitivity analysis. Scenarios represented deliberately specified alternative model structures or policy frames, while PSA represented joint parameter uncertainty around the base-case model structure [23,28].

Deterministic Sensitivity Analysis, Probabilistic Sensitivity Analysis, and Threshold Analysis

One-way deterministic sensitivity analysis varied selected high-impact parameters across prespecified bounds while holding other inputs at their base-case values. Parameters included ibogaine program cost, late-remission relapse, transition into monitored ibogaine, post-acute remission, monitored safety escalation, and comparator routing assumptions.

Probabilistic sensitivity analysis jointly varied uncertain parameters across their assigned distributions using 5000 simulations with a fixed random seed. PSA outputs included the cost-effectiveness plane, cost-effectiveness acceptability curve, parameter diagnostics, and centering checks. Willingness-to-pay thresholds were set at $50,000, $100,000, and $150,000 per QALY.

Threshold analysis focused on ibogaine program cost because medically monitored implementation cost is a central source of economic uncertainty. The threshold analysis varied program cost across prespecified values and estimated where the intervention ceased to be direct-medical-cost-saving and how net monetary benefit changed across the cost range. These analyses were included to distinguish uncertainty about clinical benefit from uncertainty about the cost of monitored implementation [11,28].

Calibration, Benchmarking, and Validation

The model was evaluated using calibration targets, external benchmark checks, and internal validation checks. Calibration targets included return to opioid use within 24 hours after ibogaine, QTc greater than 500 ms during monitored administration, and 1-month opioid-free response after ibogaine. Benchmark checks included Tennessee-specific and broader OUD treatment-cascade, mortality, and pathway-surface comparisons. Internal validation checks assessed schema validity, structural consistency, cohort mass balance, finite and nonnegative outputs, monotonic cumulative cost and QALY accumulation, bounded survival and mortality, uncertainty readiness, and scenario-readiness.

In the finalized export, schema and structural validation passed without failures. Calibration targets were met for return to opioid use within 24 hours and QTc greater than 500 ms during monitored administration. The 1-month opioid-free share remained above the calibration target and was retained as a residual uncertainty marker rather than tuned away. External benchmark deviations in selected treatment-share and survival targets were likewise retained as evidence of transportability and calibration uncertainty. This validation approach follows model-transparency recommendations that economic models should report not only selected outputs but also structure, assumptions, calibration behavior, validation checks, and residual discrepancies [29].

Shared-core semi-Markov state-transition structure used for the Tennessee opioid use disorder economic evaluation. The diagram shows the common clinical architecture underlying the analysis, including heterogeneous standard-of-care routing through methadone, buprenorphine, XR-naltrexone, non-MOUD treatment, and untreated active use; the monitored ibogaine pathway; post-acute stabilization; early remission and stable recovery; hospitalization; recent dropout or tolerance-loss risk; and death. This figure is conceptual and depicts model structure rather than realized arm-specific transition frequencies.

Base-case comparative outcomes over the 10-year Tennessee publication horizon for realistic limited-access ibogaine versus the matched no-ibogaine reference. Panel A shows cumulative incremental direct medical cost, illustrating the front-loaded cost of the ibogaine strategy followed by later cost offset. Panel B shows

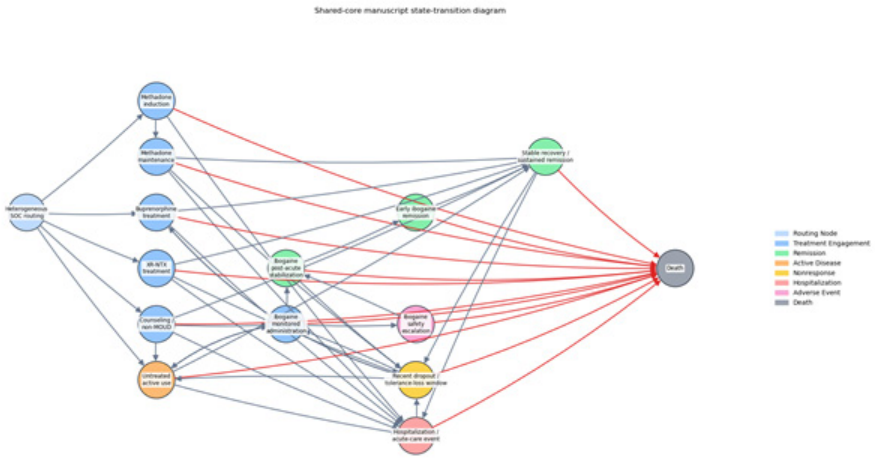

Figure 1: Shared-core state-transition structure for the Tennessee opioid use disorder model.

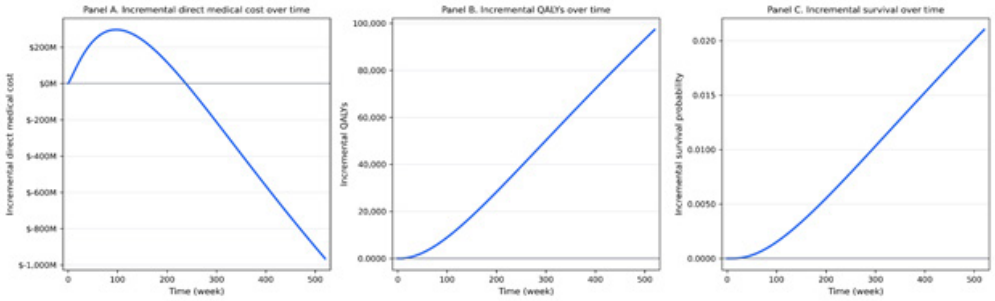

Figure 2: Base-case comparative outcomes over time for realistic limited-access ibogaine versus no-ibogaine reference.

cumulative incremental quality-adjusted life-years (QALYs). Panel C shows incremental survival probability. Negative values in Panel A favor ibogaine on the primary healthcare-sector cost endpoint.

RESULTS

Base-case analysis

In the Tennessee 10-year healthcare-sector base case, realistic limited-access ibogaine was associated with lower cumulative direct medical cost, greater QALY accrual, and higher survival than the matched no-ibogaine reference.

Cumulative direct medical cost was $5.46 billion in the ibogaine arm and $6.42 billion in the no-ibogaine reference arm, yielding an incremental direct-cost difference of -$965.0 million. Total QALYs were 627,371 in the ibogaine arm and 530,144 in the reference arm, corresponding to an incremental gain of 97,227 QALYs. Ten-year survival probability was 0.9308 with ibogaine and 0.9098 with no ibogaine, an absolute survival gain of 0.0210, or 2.10 percentage points. Mortality probability was correspondingly lower in the ibogaine arm, 0.0692 versus 0.0902.

Because the ibogaine strategy was both less costly and more effective in the base case, it was dominant relative to the no-ibogaine reference. Blended total cost, which included indirect costs and was secondary to the healthcare-sector endpoint, was also lower with ibogaine: $17.28 billion versus $27.45 billion, an incremental difference of -$10.18 billion.

Mechanistic model outputs

The arm-level event summaries were consistent with the aggregate base-case findings. Compared with the no-ibogaine reference, the realistic limited-access ibogaine arm produced more cumulative stable-recovery entries, fewer hospitalization entries, and fewer deaths over the modeled horizon.

Stable-recovery entries were 152,492 in the ibogaine arm versus 35,604 in the no-ibogaine reference. Hospitalization entries were 57,581 versus 91,667, respectively. Cumulative deaths were 7,338 in the ibogaine arm and 9,565 in the reference arm. These entry counts represent cumulative deterministic transition events rather than unique individuals, and repeat entries were permitted by the semi-Markov structure.

The baseline Tennessee routing mix was identical in both arms: 5.0% methadone, 22.0% buprenorphine, 1.5% extended-release naltrexone, 23.5% non-MOUD treatment, and 48.0% untreated or not engaged. In the ibogaine-enabled arm, cumulative entries into monitored ibogaine arose mainly from untreated active use, with smaller contributions from non-MOUD treatment and recent-dropout states. This pattern supports the interpretation that the modeled benefit was driven by movement from higher-risk states into monitored ibogaine, remission, and stable recovery, rather than by a change in the initial standard-care allocation.

Scenario analyses

Scenario analyses showed that the direction of the base-case result was generally robust to comparator-mix variation and waning efficacy, but sensitive to more pessimistic assumptions about durability, comparator performance, and monitored-care cost.

Under waning efficacy, the ibogaine strategy remained less costly and more effective than the matched reference, with incremental direct medical cost of -$152.7 million and an incremental gain of 79,539 QALYs. Under comparator-mix variation, results were close to the base case, with incremental direct medical cost of -$956.2 million

and an incremental gain of 96,592 QALYs.

The publication stress test reversed the direct-cost advantage but preserved substantial health gains. In that scenario, ibogaine increased direct medical cost by $232.7 million but produced an additional 68,547 QALYs and a survival gain of 0.012. The retreatment or re-engagement scenario had minimal incremental effect in the current implementation, with direct medical cost savings of $3.1 million and 314 additional QALYs. The short-horizon scenario showed the expected front-loaded cost pattern: ibogaine increased direct medical cost by $13.8 million over the immediate period and produced only 2.7 additional QALYs.

Overall, the scenario results suggest that the modeled value of ibogaine was not captured within the immediate post-administration window alone. The favorable long-horizon result depended on downstream changes in remission, relapse, hospitalization, and mortality over time.

Deterministic sensitivity analysis

One-way deterministic sensitivity analysis identified ibogaine program cost, late-remission relapse, and entry from untreated active use into monitored ibogaine as the most influential parameters.

Across the bounds examined, ibogaine program cost shifted incremental direct medical cost from -$1.89 billion to +$940.6 million, while leaving incremental QALYs unchanged because the analysis varied cost alone. Late-remission relapse shifted incremental direct medical cost from -$1.95 billion to -$393.5 million and shifted incremental QALYs from 109,702 to 72,142. Entry from untreated active use into monitored ibogaine had the largest effect on QALYs, shifting incremental QALYs from 46,054 to 134,802.

Other influential parameters included post-acute transition to early remission and monitored safety escalation. Comparator routing parameters had smaller effects over the tested ranges. These results indicate that the economic conclusion was most sensitive to implementation cost and durability, while the health conclusion was most sensitive to uptake into the monitored ibogaine pathway and relapse after remission.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted with 5000 simulations. The mean incremental direct medical cost was -$465.9 million, and the median was -$573.3 million. The 2.5th to 97.5th percentile interval ranged from -$1.85 billion to +$1.41 billion. Mean incremental QALYs were 93,256, with a median of 91,728 and a 2.5th to 97.5th percentile interval of 46,964 to 147,408.

Across PSA draws, 72.9% were direct-medical-cost-saving, and 100% produced positive incremental QALYs. At willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY, the ibogaine strategy was cost-effective in 99.98%, 100%, and 100% of simulations, respectively.

The deterministic base case was within 1 standard deviation of the PSA cloud center for both incremental direct medical cost and incremental QALYs, and no registry drift was detected. This supported the interpretation that the deterministic result was consistent with the probabilistic uncertainty surface rather than being an outlying configuration.

Threshold analysis

Threshold analysis focused on ibogaine program cost. At a program cost of $3,000, ibogaine was associated with direct medical cost savings of $1.89 billion. At $7,000, direct medical cost savings were $948.4 million. At $11,000, the strategy remained approximately cost-saving, with an incremental direct-cost difference of -$3.9 million. At $15,000, direct medical cost became positive, with an incremental direct-cost difference of +$940.6 million.

Because this threshold analysis varied program cost alone, incremental QALYs remained unchanged at 97,227 across the explored cost range. Net monetary benefit remained positive across the full range examined at a willingness-to-pay threshold of $100,000 per QALY. These findings suggest that the main threshold uncertainty was not whether modeled health gains persisted, but whether monitored implementation could be delivered at a cost low

Table 1. Base-case comparative outcomes

Outcome	Realistic Tennessee limited-access ibogaine	No-ibogaine reference	Incremental
Direct Medical Cost	$5,455,424,226	$6,420,473,682	$-965,049,455
Blended Total Cost	$17,277,666,900	$27,453,961,347	$-10,176,294,447
Total QALYs	627,371.32	530,144.39	97,226.93
Survival Probability	0.931	0.910	0.021
Mortality Probability	0.069	0.090	-0.021
ICER ($/QALY)	Dominant	—	—
Interpretation	Realistic Tennessee limited-access ibogaine dominates (lower cost, higher QALYs)	—	—

Note: Direct medical cost is the primary healthcare-sector cost endpoint. Blended total cost includes indirect costs and is reported as a secondary quantity.

Table 1: Base-case comparative outcomes for realistic limited-access ibogaine versus no-ibogaine reference in Tennessee.

Table 2. Scenario analyses

Scenario	Incremental direct medical cost	Incremental QALYs	Incremental survival probability
Realistic publication variant	$-965,049,455	97,226.93	0.021
Waning efficacy	$-152,655,870	79,538.65	0.015
Comparator mix variation	$-956,247,964	96,592.09	0.021
Publication stress test	$232,728,723	68,547.12	0.012
Retreatment / re-engagement	$-3,110,439	314.25	0.000
Short horizon	$13,757,716	2.71	0.000

Note: Incremental values are differences between intervention and the matched reference comparator. Full per-scenario detail (including intervention and reference arm outcomes) appears in the supplement.

Table 2: Scenario analyses for realistic limited-access ibogaine versus no-ibogaine reference.

enough to remain direct-medical-cost-saving.

Calibration and benchmark checks

The finalized Tennessee model completed prespecified structural, numerical, and cohort-balance checks without failed validation status. Calibration reproduced the monitored-safety targets for return to opioid use within 24 hours after ibogaine and QTc greater than 500 ms during monitored administration. The modeled 1-month opioid-free share after ibogaine remained above the calibration target, and selected external benchmark comparisons showed residual deviation, particularly for long-horizon survival relative to a broad OUD face-validity range. These discrepancies were retained as markers of residual uncertainty rather than tuned away. Detailed calibration, benchmark, and validation outputs are reported in the supplementary materials.

Base-case 10-year comparative outcomes for realistic limited-access ibogaine versus the matched no-ibogaine reference in the Tennessee publication analysis. Direct medical cost is the primary healthcare-sector cost endpoint. Blended total cost, which includes indirect costs under the current implementation, is reported as a secondary quantity.

Scenario analyses for the Tennessee publication model. Reported values show the incremental difference between realistic limited-access ibogaine and the matched no-ibogaine reference under each scenario. Incremental direct medical cost is the primary healthcare-sector cost endpoint; incremental QALYs and incremental survival are shown to summarize comparative health impact.

DISCUSSION

In this Tennessee-focused decision-analytic study, adding a medically monitored ibogaine pathway to heterogeneous standard care was associated with lower direct medical cost, greater QALY accrual, and higher survival over a 10-year healthcare-sector horizon. The base-case result was economically favorable because the intervention was both less costly and more effective than the matched no-ibogaine reference. The more important interpretation, however, is not that ibogaine is guaranteed to be cost-saving under all plausible assumptions. Rather, the model suggests that a monitored ibogaine pathway could plausibly generate enough downstream reduction in relapse, hospitalization, disengagement, and mortality to offset substantial front-loaded implementation costs in a high-burden state treatment environment.

The time pattern of results is central to interpretation. In the short-horizon scenario, ibogaine increased direct medical cost and produced minimal QALY gain, as expected for an intervention with up-front program, monitoring, and post-acute costs. The base-case advantage emerged over longer follow-up, as more patients entered remission or stable recovery and fewer entered hospitalization or death. This pattern is consistent with the broader OUD treatment literature, in which economic value is shaped less by isolated detoxification events than by treatment engagement, retention, reduced acute-care utilization, overdose protection, and sustained recovery [3,4,11].

The comparator structure is also important. This was not a comparison of ibogaine against an untreated control group, nor a head-to-head comparison against optimized buprenorphine treatment among already-engaged patients. Both arms began with the same Tennessee treatment-cascade allocation, including methadone, buprenorphine, extended-release naltrexone, non-MOUD treatment, and untreated or not-engaged care. The ibogaine-enabled arm differed only by allowing eligible transitions into medically monitored ibogaine from selected clinical states. The untreated share therefore represents a baseline feature of the Tennessee treatment environment, not an artificial penalty imposed on the comparator arm. This distinction matters because Tennessee's decision problem is not whether ibogaine should replace established MOUD, but whether an additional monitored pathway could improve outcomes for a subset of patients who otherwise remain untreated, undertreated, or poorly retained in care.

The scenario analyses clarify where the result is robust and where it remains vulnerable. Comparator-mix variation produced results close to the base case, suggesting that the primary finding was not driven solely by a narrow standard-care routing assumption. Waning efficacy attenuated the economic advantage but did not eliminate the health gain. The conservative stress test reversed direct medical cost savings, but the intervention still produced substantial QALY gains and improved survival. This pattern is policy-relevant: under more pessimistic assumptions, medically monitored ibogaine shifted from cost-saving to higher-cost but more effective, rather than becoming clinically neutral or harmful in the model. That is a more informative conclusion than a binary "cost-saving or not" claim, because early implementation decisions often ask whether an intervention plausibly improves outcomes at an acceptable cost while additional prospective evidence is generated.

Cardiac toxicity is a central boundary condition for this interpretation. The modeled intervention was medically monitored ibogaine, not unsupervised ibogaine exposure or a low-resource detoxification episode. The pathway included screening, monitored administration, safety-escalation capacity, and post-acute follow-up because ibogaine has known cardiac safety concerns, including QTc prolongation and proarrhythmic liability [16-19]. In economic terms, monitoring and escalation capacity are not optional add-ons; they define the intervention being evaluated. A lower-cost implementation model that removed cardiac monitoring would represent a different and less defensible intervention and should not inherit the present results.

The threshold analysis reinforces this point. Ibogaine program cost was one of the most influential drivers of incremental direct medical cost. At lower program-cost values, the intervention remained strongly cost-saving; at higher values, cost savings narrowed or reversed. QALY gains were unchanged in the program-cost threshold analysis because the analysis varied cost alone. This indicates that the central implementation uncertainty is not only whether ibogaine can produce clinical benefit, but whether medically monitored delivery can be organized at a cost compatible with Tennessee's healthcare-sector priorities. In a state program, pilot, or clinical-trial infrastructure, collecting protocol-specific cost data should therefore be treated as a primary empirical objective rather than a secondary administrative detail.

These findings are timely because Tennessee and federal policymakers are actively considering mechanisms for structured psychedelic and ibogaine-related research. The Tennessee HOPE Treatment Act creates a state-level framework for ibogaine drug-development clinical trials, while recent federal policy has signaled interest in improving access pathways and evidence generation for investigational psychedelic therapies, including ibogaine compounds [20,21]. The present model does not establish that ibogaine should be adopted as routine OUD care. It does suggest that, if Tennessee proceeds with a monitored clinical-trial or implementation program, health-economic endpoints

should be embedded prospectively. Those endpoints should include protocol-specific program cost, monitoring and escalation cost, acute-care utilization, relapse, remission durability, overdose events, mortality, and post-acute treatment engagement.

Several limitations should temper interpretation. First, the ibogaine clinical evidence base remains limited, observational, and protocol-sensitive. Inputs for early response, relapse, and durability necessarily relied on nonrandomized follow-up and safety studies rather than large randomized comparative-effectiveness trials [13-15,18]. Second, Tennessee pathway shares remain partly assumption-based. The model incorporated Tennessee-specific denominator and overdose-context anchors, and it reflected a buprenorphine-heavy, methadone-constrained state treatment environment, but no single public source provides a definitive all-payer split across methadone, buprenorphine, extended-release naltrexone, non-MOUD treatment, and untreated care. Third, several cost inputs remain localizable and implementation-sensitive, including ibogaine program cost, monitored-care cost, safety-escalation cost, comparator-pathway costs, and hospitalization or overdose-event cost.

Fourth, model calibration and benchmarking were supportive but not perfect. The model reproduced the prespecified monitored-safety targets for immediate return to opioid use and QTc greater than 500 ms during monitored administration, but the modeled 1-month opioid-free share remained above the calibration target. Selected external benchmark comparisons also showed residual deviation, including long-horizon survival relative to a broad OUD face-validity range. These discrepancies were retained rather than tuned away. That choice makes the analysis more conservative from a reporting standpoint, because it acknowledges that the model remains dependent on uncertain long-run ibogaine durability and transportability assumptions.

Fifth, this analysis does not argue that ibogaine should displace methadone or buprenorphine. Those treatments have stronger evidence bases, established mortality benefits, and existing delivery infrastructure [3,4,11,30]. The modeled question is narrower: whether adding a monitored ibogaine pathway to Tennessee's existing care environment could plausibly improve health outcomes and reduce or justify costs under explicit assumptions. Future work should compare alternative implementation designs, identify subgroups most likely to benefit, and evaluate whether ibogaine functions best as an adjunctive pathway, a post-discontinuation rescue pathway, or a structured bridge into ongoing evidence-based OUD care.

The main empirical priorities are now clear. Prospective Tennessee implementation or clinical-trial data should measure not only abstinence or withdrawal outcomes, but also cardiac monitoring results, serious adverse events, post-acute engagement, relapse timing, acute-care utilization, and patient-level predictors of response. Economic data collection should be embedded from the outset, including itemized program costs, monitoring intensity, escalation events, aftercare costs, and payer-relevant utilization. Such data would reduce dependence on assumption-driven inputs and allow future analyses to replace localizable placeholder costs and routing assumptions with observed Tennessee-specific estimates.

Overall, the model supports further prospective evaluation of medically monitored ibogaine in Tennessee. It does not establish ibogaine as standard OUD treatment, and it does not reduce the need for rigorous clinical, safety, regulatory, and implementation evidence. It does indicate that, when modeled as a medically intensive pathway with explicit cardiac monitoring and safety escalation, ibogaine may have enough potential health and economic value to justify structured evaluation in a state-level program.

CONCLUSION

In this Tennessee-specific semi-Markov cost-effectiveness analysis, adding a medically monitored ibogaine pathway to heterogeneous standard care was associated with lower direct medical cost, higher QALYs, and improved survival over a 10-year healthcare-sector horizon. The base-case strategy was dominant relative to the matched no-ibogaine reference, but the magnitude and economic direction of benefit depended on assumptions about program cost, durability, uptake, and comparator performance.

The central implication is not that ibogaine is ready for routine implementation or that it should replace established medications for OUD. Rather, the findings suggest that a carefully monitored Tennessee ibogaine clinical-trial or implementation pathway could be economically plausible if it improves sustained recovery and reduces downstream hospitalization, relapse, and mortality risk. Because cardiac safety monitoring and escalation capacity are integral to the modeled intervention, future programs should collect prospective safety, clinical, utilization, and cost data sufficient to test whether these modeled benefits are realized in practice.

REFERENCES

1. Dowell D, Brown S, Gyawali S, et al. Treatment for Opioid Use Disorder: Population Estimates - United States, 2022. MMWR Morb Mortal Wkly Rep. 2024; 73: 567-574.
2. Wakeman SE, Larochelle MR, Ameli O, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open. 2020; 3: e1920622.
3. Santo T Jr, Clark B, Hickman M, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021; 78: 979-993.
4. Krawczyk N, Mojtabai R, Stuart EA, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. Addiction. 2020; 115: 1683-1694.
5. https://www.med.unc.edu/fammed/nctac/wp-content/uploads/sites/1256/2025/09/2024-nsduh-companion-report.pdf
6. https://www.tn.gov/content/dam/tn/health/documents/pdo/death-report/2023_Tennessee_Drug_Overdose_Death_Report.pdf
7. https://www.tn.gov/content/dam/tn/health/documents/pdo/legislative-report/Drug_Overdose_Hospital_Discharges_Report_2025.pdf
8. https://www.tn.gov/content/dam/tn/tenncare/documents/BESMARTProgramDescription.pdf
9. https://healthdata.tn.gov/Behavioral-Health/Buprenorphine-Report-2020/ubtb-p6q9
10. Fairley M, Humphreys K, Joyce VR, et al. Cost-effectiveness of Treatments for Opioid Use Disorder. JAMA Psychiatry. 2021; 78: 767-777.
11. Qian G, Humphreys K, Goldhaber-Fiebert JD, et al. Estimated effectiveness and cost-effectiveness of opioid use disorder treatment under proposed U.S. regulatory relaxations: A model-based analysis. Drug Alcohol Depend. 2024; 256: 111112.
12. Brown TK, Alper K. Treatment of opioid use disorder with ibogaine: detoxification and drug use outcomes. Am J Drug Alcohol Abuse. 2018; 44: 24-36.

13. Mash DC, Duque L, Page B, et al. Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes. Front Pharmacol. 2018; 9: 529.
14. Noller GE, Frampton CM, Yazar-Klosinski B. Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. Am J Drug Alcohol Abuse. 2018; 44: 37-46.
15. Köck P, Froelich K, Walter M, et al. A systematic literature review of clinical trials and therapeutic applications of ibogaine. J Subst Abuse Treat. 2022; 138: 108717.
16. Mosca A, Chiappini S, Miuli A, et al. Ibogaine/Noribogaine in the Treatment of Substance Use Disorders: A Systematic Review of the Current Literature. Curr Neuropharmacol. 2023; 21: 2178-2194.
17. Knuijver T, Schellekens AFA, Belgers M, et al. Safety of ibogaine administration in detoxification of opioid-dependent individuals: a descriptive open-label observational study. Addiction. 2022; 117: 118-128.
18. Koenig X, Kovar M, Boehm S, et al. Anti-addiction drug ibogaine inhibits hERG channels: a cardiac arrhythmia risk. Addict Biol. 2014; 19: 237-239.
19. Walley P. Helping Open Pathways to Effective (HOPE) Treatment Act. 2026.
20. https://www.whitehouse.gov/fact-sheets/2026/04/fact-sheet-president-donald-j-trump-is-accelerating-medical-treatments-for-serious-mental-illness
21. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022; 25: 3-9.
22. Siebert U, Alagoz O, Bayoumi AM, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–3. Med Decis Making. 2012; 32: 690-700.
23. Florence CS, Zhou C, Luo F, et al. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Med Care. 2016; 54: 901-906.
24. Wittenberg E, Bray JW, Aden B, et al. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. Addiction. 2016; 111: 675-684.
25. Nosyk B, Bray JW, Wittenberg E, et al. Short term health-related quality of life improvement during opioid agonist treatment. Drug Alcohol Depend. 2015; 157: 121-128.
26. Patton T, Boehnke JR, Goyal R, et al. Analyzing quality of life among people with opioid use disorder from the National Institute on Drug Abuse Data Share initiative: implications for decision making. Qual Life Res. 2024; 33: 2783-2796.
27. Briggs AH, Weinstein MC, Fenwick EAL, et al. Model Parameter Estimation and Uncertainty Analysis: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–6. Med Decis Making. 2012; 32: 722-732.
28. Eddy DM, Hollingworth W, Caro JJ, et al. Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. Med Decis Making. 2012; 32: 733-743.
29. Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. The Lancet. 2018; 391: 309-318.