SUPPLEMENTARY MATERIALS

Cost-Effectiveness of Tonic Motor Activation (TOMAC) Therapy for Patients with Restless Legs Syndrome: An Exploratory Analysis

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S.1: Search Terms and Literature Review

An informal literature search was conducted in Pubmed, in order to identify relevant published RLS cost, health-related quality of life, and resource utilization data. The keywords relied upon are detailed in Table S.1.1, while the search strategy is summarized in Table S.1.2. This systematic search was supplemented with additional literature searches and the identification of texts from relevant systematic reviews, resulting in the final number of n=45 relevant RLS texts identified.

Table S.1.1: Keywords relied upon in Systematic Search

Keywords
“restless leg*”, “RLS”, “Willis Ekborn*”, “Restless leg syndrome”, “IRLS”, “restless”
“cost”, “resource use”, “resource utilization”, “healthcare resource”, “health”
“health-related quality*”, “quality of life”, “utility”, “EQ-5D”

Table S.1.1: Summary of Search Strategy

Set #	**Terms**
#1	("economics"[MeSH Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) AND ("health resources"[MeSH Terms] OR ("health"[All Fields] AND "resources"[All Fields]) OR "health resources"[All Fields] OR "resource"[All Fields] OR "resources"[All Fields] OR "resource s"[All Fields] OR "resourced"[All Fields] OR "resourceful"[All Fields] OR "resourcefulness"[All Fields] OR "resourcing"[All Fields] OR (("health resources"[MeSH Terms] OR ("health"[All Fields] AND "resources"[All Fields]) OR "health resources"[All Fields] OR "resource"[All Fields] OR "resources"[All Fields] OR "resource s"[All Fields] OR "resourced"[All Fields] OR "resourceful"[All Fields] OR "resourcefulness"[All Fields] OR "resourcing"[All Fields]) AND ("statistics and numerical data"[MeSH Subheading] OR ("statistics"[All Fields] AND "numerical"[All Fields] AND "data"[All Fields]) OR "statistics and numerical data"[All Fields] OR "utilization"[All Fields] OR "utilisation"[All Fields] OR "utilisations"[All Fields] OR "utilise"[All Fields] OR "utilised"[All Fields] OR "utilises"[All Fields] OR "utilising"[All Fields] OR "utilities"[All Fields] OR "utility"[All Fields] OR "utilizations"[All Fields] OR "utilize"[All Fields] OR "utilized"[All Fields] OR "utilizer"[All Fields] OR "utilizers"[All Fields] OR "utilizes"[All Fields] OR "utilizing"[All Fields])) OR (("delivery of health care"[MeSH Terms] OR ("delivery"[All Fields] AND "health"[All Fields] AND "care"[All Fields]) OR "delivery of health care"[All Fields] OR "healthcare"[All Fields] OR "healthcare s"[All Fields] OR "healthcares"[All Fields]) AND ("health resources"[MeSH Terms] OR ("health"[All Fields] AND "resources"[All Fields]) OR "health resources"[All

	Fields] OR "resource"[All Fields] OR "resources"[All Fields] OR "resource s"[All Fields] OR "resourced"[All Fields] OR "resourceful"[All Fields] OR "resourcefulness"[All Fields] OR "resourcing"[All Fields])) OR ("health"[MeSH Terms] OR "health"[All Fields] OR "health s"[All Fields] OR "healthful"[All Fields] OR "healthfulness"[All Fields] OR "healths"[All Fields]))
#2	(("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "restlessness"[All Fields] OR "restless"[All Fields]) AND "leg"[All Fields]) OR "RLS"[All Fields] OR (("willis"[All Fields] OR "willis s"[All Fields]) AND "ekborn*"[All Fields]) OR ("restless legs syndrome"[MeSH Terms] OR ("restless"[All Fields] AND "legs"[All Fields] AND "syndrome"[All Fields]) OR "restless legs syndrome"[All Fields] OR ("restless"[All Fields] AND "leg"[All Fields] AND "syndrome"[All Fields]) OR "restless leg syndrome"[All Fields]) OR "IRLS"[All Fields] OR ("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "restlessness"[All Fields] OR "restless"[All Fields])
#3	(#1) AND (#2)
#4	("health-related"[All Fields] AND "quality*"[All Fields]) OR ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR ("statistics and numerical data"[MeSH Subheading] OR ("statistics"[All Fields] AND "numerical"[All Fields] AND "data"[All Fields]) OR "statistics and numerical data"[All Fields] OR "utilization"[All Fields] OR "utilisation"[All Fields] OR "utilisations"[All Fields] OR "utilise"[All Fields] OR "utilised"[All Fields] OR "utilises"[All Fields] OR "utilising"[All Fields] OR "utilities"[All Fields] OR "utility"[All Fields] OR "utilizations"[All Fields] OR "utilize"[All Fields] OR "utilized"[All Fields] OR "utilizer"[All Fields] OR "utilizers"[All Fields] OR "utilizes"[All Fields] OR "utilizing"[All Fields]) OR "EQ-5D"[All Fields]
#5	(#2) AND (#4)
#6	(#3) AND (#5)

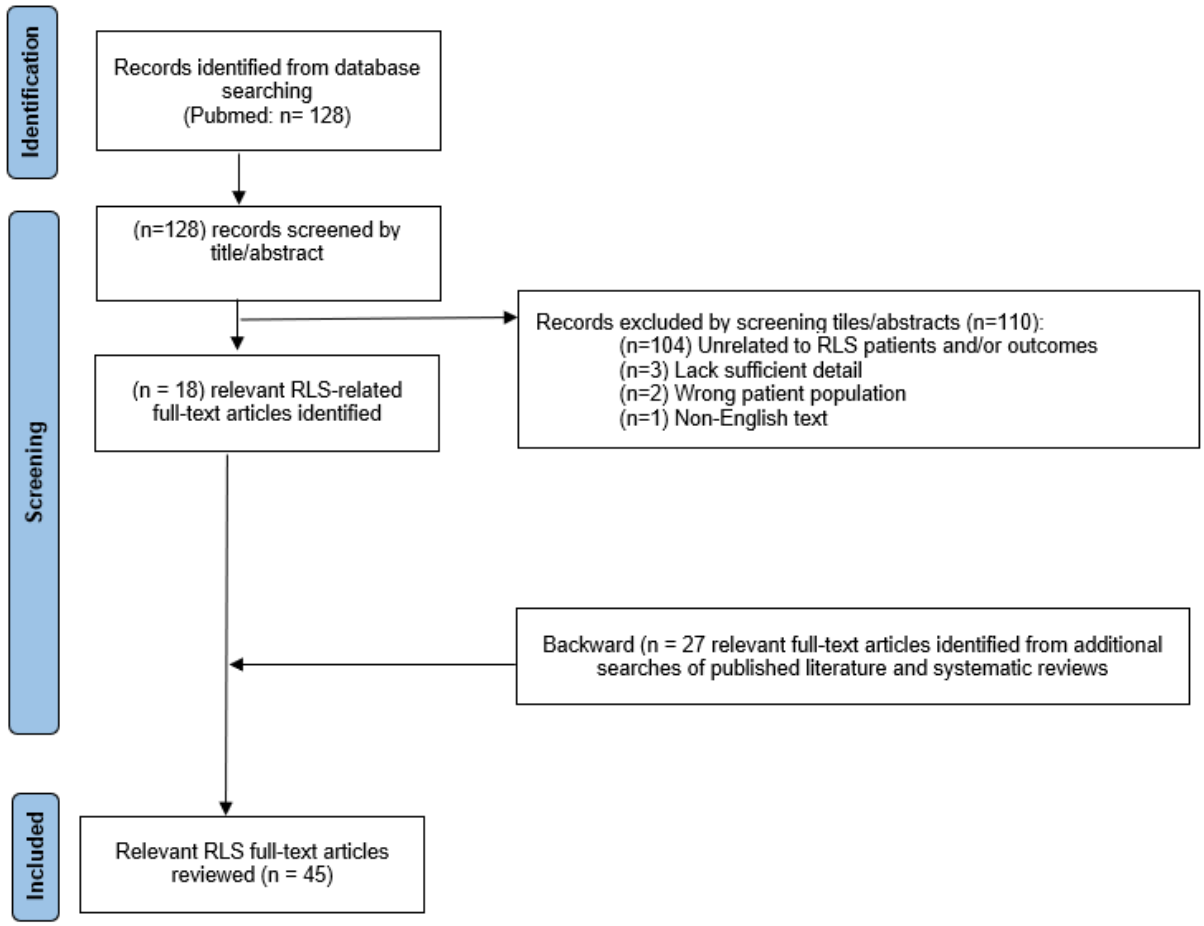


Figure S.1.1: PRISMA flowchart detailing the literature search strategy.

Legend: RLS: Restless legs syndrome

**From the N=45 texts reviewed, a sample of relevant texts informed key model inputs and ranges explored in sensitivity analyses. The additional texts provided useful contextual information that aided in the development of, and inspired commentary detailed in the manuscript.*

S.2: Derivation of Health-related Quality of Life Utility Estimates

Two relevant sources of published data, Happe et al. and Lees et al., provided EQ-5D utility estimates by IRLS severity. Both relied upon the International RLS Study Group Rating Scale (IRLS) to classify RLS severity, utilizing the midpoint of each of the reported IRLS severity ranges. The classification employed by Lees et al. was different than that recommended by the International RLS Study Group. Mild, moderate, severe, and very severe RLS ranged from 1-14, 15-24, 25-34, and 35-40, respectively, from Lees et al. (18). Whereas, the International RLS Study group recommended 1-10, 11-20, 21-30, and 31-40 as mild, moderate, severe, and very severe, respectively (25).

Both studies surveyed a population consisting of only RLS patients, meaning it is not possible to estimate the impact of RLS alone on HRQoL outcomes, as neither study controlled for the presence of comorbidities. Lees et al. dispersed a mail-in survey, where only 83 out of 250 participants responded (18). In addition, the sample included in Happe et al. were patients who had been referred to a specialty neurologist or clinic for RLS (17).

The underlying cohort characteristics for both Happe et al. and Lees et al. were compared to the RESTFUL cohort. Cohort characteristics were minimally addressed in Lees et al., but the cohort included in Happe et al. is relatively comparable to the RESTFUL cohort in age, gender composition, and disease severity. Summarized cohort characteristics, where reported, can be reviewed in Table S.2.1 below.

Table S.2.1: Summarized Cohort Characteristics

	RESTFUL Cohort	Happe et al.	Lees et al.
Total, n	133	519	83
Age, years	57.4	64.2 +/- 11.1	Not reported.
Percent Male, %	39.8%	37%	Not reported.

Duration of Disease, years	11.4*	18.7 +/- 14.5	Not reported.
Mean IRLS Sum Score	25.3	22.7 +/- 9.8	Not reported.

**Indicates years of medication utilization.*

Regression models were fitted to each respective dataset (second-degree polynomial for Happe et al. and third-order polynomial for Lees et al.), as means to provide a function to estimate utility values based on a change in IRLS score ()(17, 18). The resulting predictive functions are detailed in Table S.2.1.

Table S.2.2: Resulting Utility Functions

Resulting Utility Functions	
Happe et al.	EQ-5D Estimate = 0.9629132 – 0.0066548*IRLS – 0.0004783 * (IRLS – 16)^2
Lees et al.	EQ-5D Estimate = (8E-06*IRLS$^{3)}$ – (0.0009*IRLS^2) + (0.0007*IRLS) + 0.9302

Table S.2.3: Four-week IRLS Scores and Corresponding Utilities

	Baseline	Sham	TOMAC	vs. Baseline	vs. Sham
IRLS Score	***25.3***	***21.6***	***18.1***	***-7.2***	***-3.4***
Happe et al.	0.75	0.8	0.84	**0.09**	**0.04**
Lees et al.	0.50	0.61	0.7	**0.2**	**0.09**

Table S.2.4: Twenty-four-week IRLS Scores and Corresponding Utilities

	TOMAC Baseline	Control	TOMAC	vs. Control
IRLS Score	***24.5***	***20.4***	***13.2***	***-5.9***
Happe et al.	0.77	0.82	0.87	**0.05**
Lees et al.	0.52	0.64	0.80	**0.16**

Tables S.2.3 and S.2.4, above, demonstrate the resulting utility estimates corresponding to the trial observed IRLS scores. The four-week change from baseline reflects the change in IRLS score for the TOMAC cohort from baseline (IRLS score reduced 25.3 to 18.1 for TOMAC (-7.2 points)), while the change from Baseline for the Sham group was 25.4 to 21.6 (-3.8 points), leading to the -3.4 between-

group effect size (6). Additional long-term data from the extension trial informed the twenty-four week effect size, which is explored in scenario analyses (14).

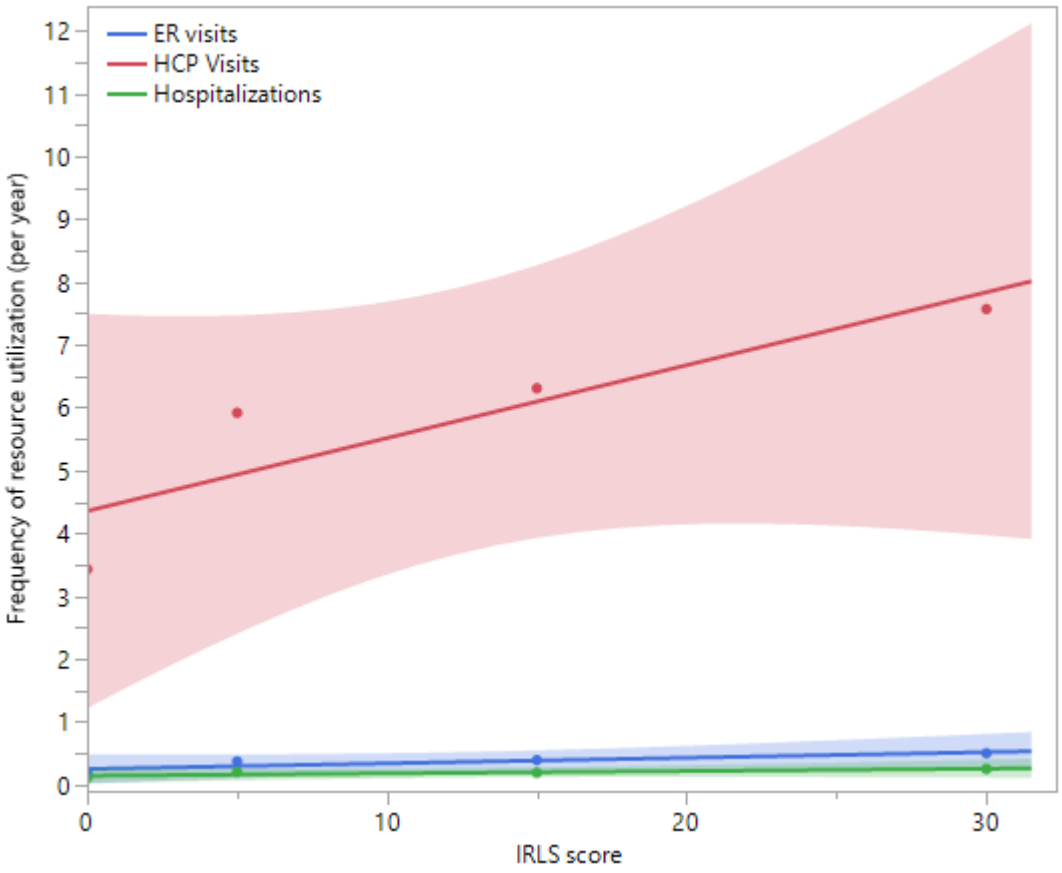
S.3: Estimating Resource Utilization based on changes in IRLS Score

Six-month resource utilization, specific to RLS severity, from Durgin et al. informed estimates relied upon in the model. Data was collected from n=904 mild, n=1,130 moderate, and n=358 RLS patients, through the 2012 administration of the US National Health and Wellness Survey (NHWS, N=71,141) (16). Similar to methods formerly discussed and relying upon the midpoints in each respective data range, regression models were fitted for each category of resource utilization – ER visits, hospitalizations, and healthcare provider visits. The resulting linear functions provided resource utilization estimates, based on changes in IRLS score. The resulting predictive functions are detailed in Table S.3.1, while the data and respective regression analyses are illustrated in the subsequent figure.

Table S.3.1: Resulting Functions

Resulting Functions	
ER Visits (six months)	ER visits = 0.2480952 + 0.0089524*IRLS
Hospitalizations (six months)	Hospitalizations = 0.1404762 + 0.0037619*IRLS
Healthcare Provider Visits (six months)	HCP = 4.3557143 + 0.1161429 * IRLS

Figure S.3.1: ER visit, Healthcare Provider visit, and Hospitalization Rates by IRLS Score



Legend: ER: Emergency room; HCP: Health care provider; IRLS: International RLS Study Group Rating Scale

The resulting annual health event rates from key modeled scenarios can be viewed in the table below. Table S.3.2 presents the health event rates corresponding to the four-week change in IRLS score reported, while S.3.3 provides the health event rates based on the long-term, twenty-four-week change in IRLS score reported in the extension trial.

Table S.3.2: Annual Health Event Rates, based on four-week IRLS Scores

	TOMAC	*Sham*	*Baseline*
ER Visits	*0.82*	*0.88*	*0.95*
Hospitalizations	*0.42*	*0.44*	*0.47*
Healthcare Provider Visits	*12.92*	*13.73*	*14.59*

Table S.3.3: Annual Health Event Rates, based on twenty-four-week IRLS Scores

	TOMAC	*Control*
ER Visits	*0.73*	*0.86*
Hospitalizations	*0.38*	*0.43*
Healthcare Provider Visits	*11.78*	*13.45*

S.4: Derivation of Monthly Medication Costs

Two different – literature and clinical trial data -- approaches to quantify monthly medication costs were explored. Similar to the aforementioned systematic search described, a separate quasi-systematic search was conducted to identify relevant literature related to standard RLS pharamcologic treatment regimens. Literature-informed RLS treatment regimens, including initial and maximum effective doses informed the medications and doses costed in the literature-based approach (5). While, reported medication utilization, from CT-04 and CT-05 trial data informed the medications and average dose costed in the clinical data approach (6). Unit costs associated with the medications and doses of interest were then sourced from fee schedule data (24). The average of the lowest and highest vendor cost informed the medication cost for each drug, respectively, with a standard adjustment factor applied to all costs to reflect U.S. healthcare system costs. Utilizing this information and approach, average monthly and annual costs were derived using a bottom-up approach.

The resulting monthly costs derived utilitizing the literatre and clinical data informed approaches were $340 and $254 respectively. One limitation of the literature cost estimate is that each medication included is equally weighted in the monthly cost derivation, which may not be reflective of real-world pharmacologic prescribing trends, especially with regards to opioid use. Ultimately, the trial-derived estimate informed the monthly medication costs in the base case, with the literature-derived estimate explored in senstivity analyses.

Table S.4.1: Summary of Literature Informed, Unadjusted Monthly Medication Cost Derivation

Alpha-2-Delta Ligands	Initial Dose	Daily Cost	Monthly Cost	Max Dose	Daily Cost	Monthly Cost
Gabapentin	300 mg	$ 3.63	$ 108.86	3600 mg	$ 30.92	$ 927.46
Pregabalin	75 mg	$ 3.69	$ 110.22	450 mg	$ 7.41	$ 221.80
Gabapentin Enacarbil	600 mg	$ 11.44	$ 343.08	600-1200 mg	$ 17.16	$ 514.61
Average		**$ 6.25**	**$ 187.38**		**$ 18.50**	**$ 554.62**
Dopamine Agonists	**Initial Dose**			**Max Dose**		
Pramipexole	0.125 mg	**	**	0.5	$ 20.31	$ 609.32
Ropinirole	0.25 mg	$0.15	$12.44	2-4 mg	$ 1.06	$ 35.83
Rotigotine Patch	1 mg	$21.72	$651.41	3 mg	$21.72	$651.41
Average		**$10.93**	**$331.92**		**$14.36**	**$432.19**
Opioids	**Initial Dose**			**Usual Effective dose**		
Tramadol	50 mg	$ 0.06	$ 1.75	100-200 mg	$ 8.65	$ 259.57
Codeine	30 mg	$ 0.32	$ 9.44	60-180 mg	$ 1.66	$ 50.08
Morphine CR	10-15 mg	$ 1.83	$ 54.95	15-45 mg	$ 4.27	$ 127.96
Oxycodone	5-10 mg	$ 2.94	$ 88.13	10-30 mg	$ 2.87	$ 86.10
Hydrocodone	10-15 mg	$ 4.30	$ 128.88	20-45 mg	$ 9.21	$ 276.20
Methadone	2.5-5 mg	$ 0.05	$ 1.47	5-20 mg	$ 0.09	$ 3.11
Average		**$ 1.58**	**$ 47.44**		**$ 4.46**	**$ 133.84**

	Unadjusted	Adjusted
Average Annual Cost	**$ 3,374.76**	**$ 4,083.46**
Average Monthly Cost	**$ 281.23**	**$340.29**

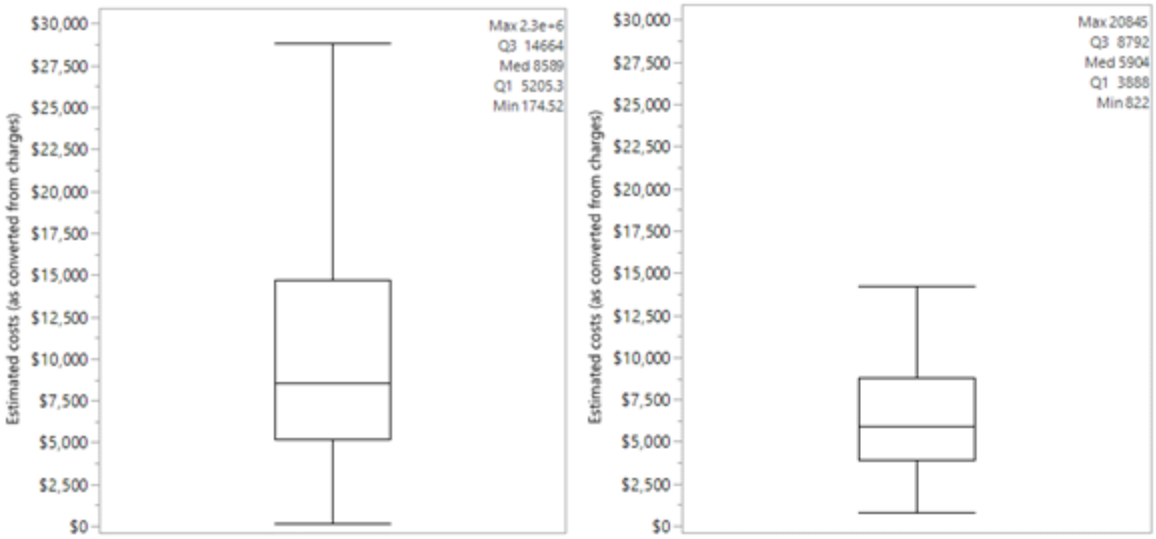
Table S.4.2: Summary of Clinical Trial Informed, Unadjusted Monthly Medication Cost Derivation

		Low Price Vendor			High Price Vendor			
	Dose Price Used	Daily Cost	Monthly Cost	Annual Cost	Daily Cost	Monthly Cost	Annual Cost	Average Annual Low-High Vendor Cost
Gabapentin	400 mg	$ 0.03	$ 0.98	$ 11.81	$ 6.47	$ 194.23	$ 2,330.71	$ 1,171.26
Gabapentin Enacarbil	600 mg	$ 11.30	$ 338.86	$ 4,066.32	$ 11.58	$ 347.29	$ 4,167.48	$ 4,116.90
Methadone	30 mg	$ 0.13	$ 3.84	$ 46.12	$ 0.61	$ 18.32	$ 219.78	$ 132.95
Oxycodone	15 mg	$ 0.08	$ 2.25	$ 27.00	$ 5.02	$ 150.49	$ 1,805.83	$ 916.42
Pramipexole	1.5 mg	$ 2.38	$ 71.53	$ 858.36	$ 23.64	$ 709.28	$ 8,511.36	$ 4,684.86
Pregabalin	150 mg	$ 0.05	$ 1.52	$ 18.24	$ 7.33	$ 219.33	$ 2,631.96	$ 1,325.10
Ropinirole	2 mg	$ 0.07	$ 2.40	$ 28.80	$ 0.22	$ 22.47	$ 269.64	$ 149.22
Rotigotine	3 mg	$ 18.42	$ 552.47	$ 6,629.64	$ 25.01	$ 750.16	$ 9,001.92	$ 7,815.78
Tramadol	50 mg	$ 3.98	$ 119.30	$ 1,431.60	$ 9.21	$ 276.34	$ 3,316.08	$ 2,373.84

	Unadjusted	Adjusted
Weighted Average Total Annual Medication Cost	**$ 1,875**	**$ 2,269.32**
Average Annual Med Cost	**$ 2,521**	**$ 3,050.05**
	Unadjusted	**Adjusted**
Weighted Average Monthly Medication Cost	$ 156.29	$ 189.11
Average Monthly Med Cost	$ 210.06	$ 254.17

S.5: Estimation of Hospitalization Costs in the Medicare Population

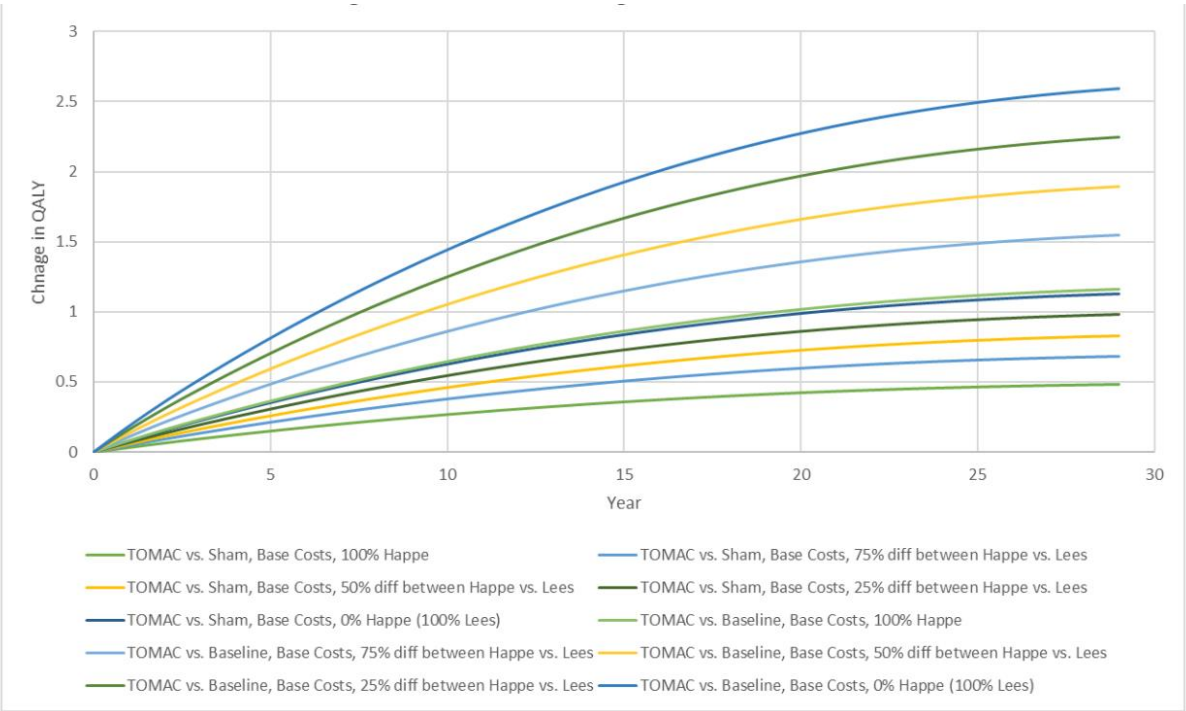
Figure S.5.1: Estimated hospitalization costs for claims with RLS as any diagnosis (left), Estimated Hospitalization costs for claims with RLS as the primary diagnosis (right)



To estimate the approximate cost of hospitalizations in the Medicare population – which frequently is used as a proxy for true cost – the CMS 2019 Medpar dataset was analyzed, identifying the subset of episodes of care where RLS was among any of the coded diagnoses, and separately the subset where RLS was coded as the primary diagnosis. The analysis was limited to traditional Medicare claims (claim type 60). Costs were calculated for each claim applying the site-specific Medicare-published global cost-to-charge ratio (CCR). Boxplots of the cost estimates are shown in Figure S.5.1, where the figure on the left depicts claims with RLS as any of the diagnoses, while the figure on the right shows claims with RLS as the primary diagnosis. The corresponding mean costs were $12,425 and $6,732, respectively. Adding professional fees on top of the facility costs and using the lower amount, as a conservative estimate, led to the adjustment factor of 40% applied to the Durgin et al. published costs (resulting in the base case hospitalization cost of $7,676).

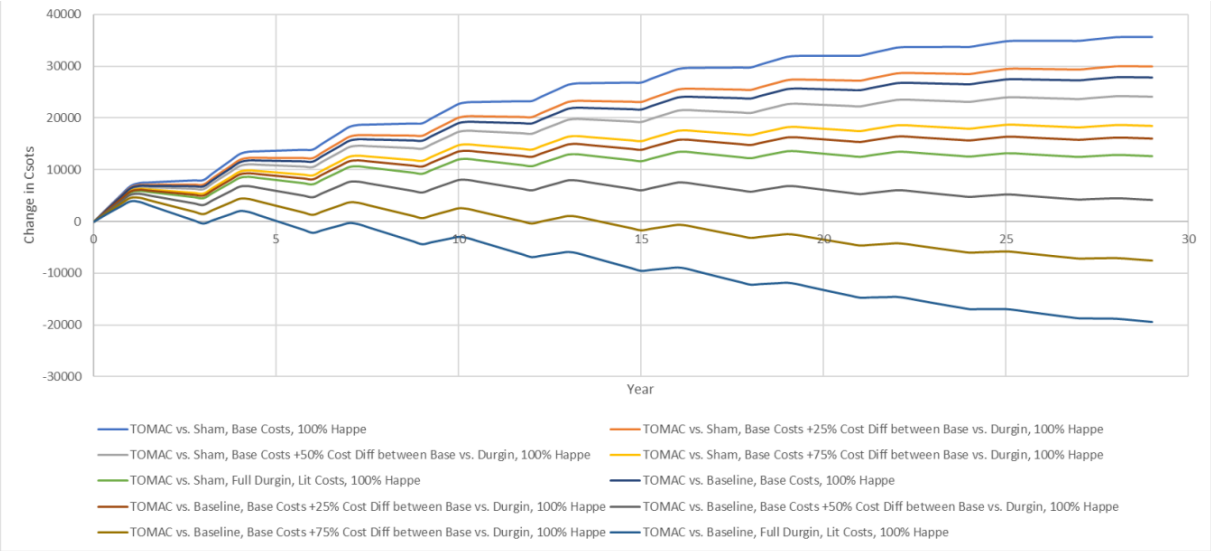
S.6: Supplemental Results & Sensitivity Analyses Explored

Figure S.6.1A: Cumulative Change in QALYs over Time



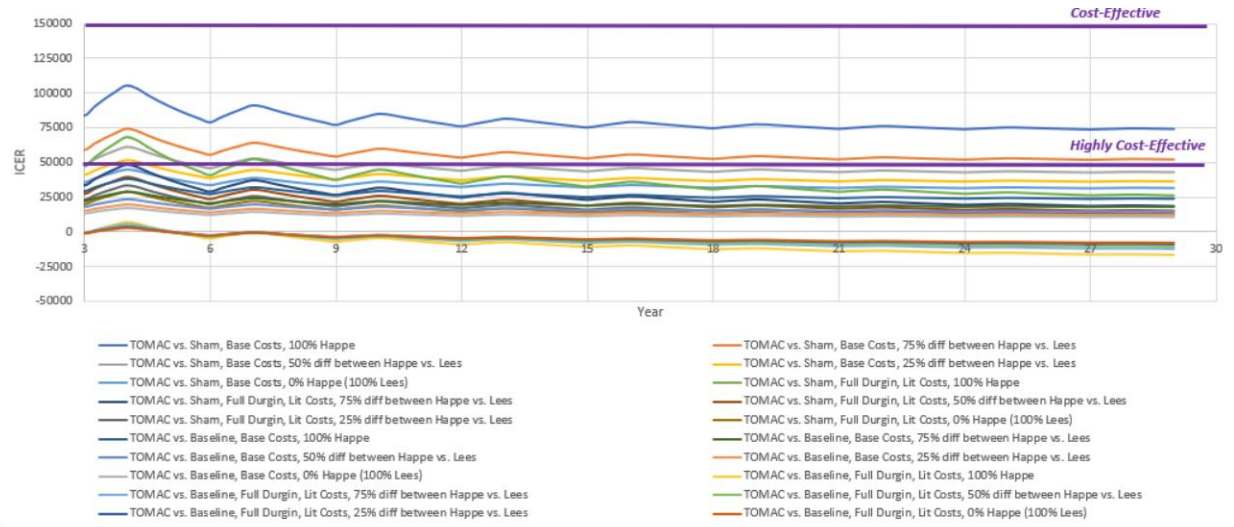
The resulting cumulative change in QALYs over time, for scenarios exploring varied cost and utility inputs, are provided in Figure S.6.1A above. This figure again communicates that the utilities informing the base case result in the most conservative projection in QALY gain with TOMAC therapy. For all scenarios exploring alternate utility inputs and relying upon the TOMAC vs. Baseline IRLS effect size, the resulting change in QALYs is much greater.

Figure S.6.1B: Cumulative Change in Costs over Time



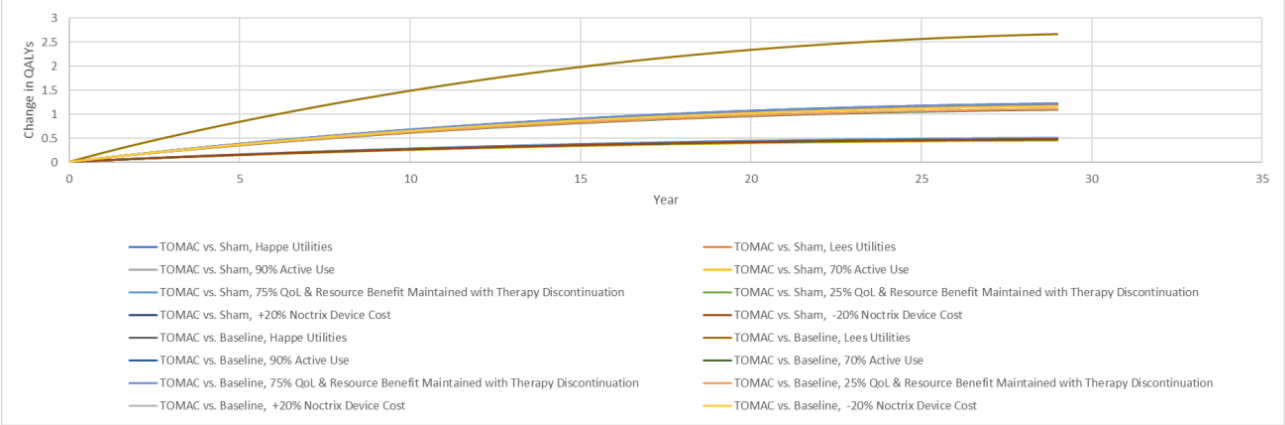
The resulting cumulative change in costs over time, for scenarios exploring varied cost and utility inputs are detailed in Figure S.6.1B above. This figure illustrates how the increased costs incurred with TOMAC are greatest in the base case, but under scenarios exploring an alternate IRLS effect size or full literature-reported health event costs, costs associated with TOMAC therapy begin to be amortized by the occurrence of fewer health events among the TOMAC cohort. In these scenarios, TOMAC therapy can even result in cost-savings.

Figure S.6.1C: Resulting ICER over Time



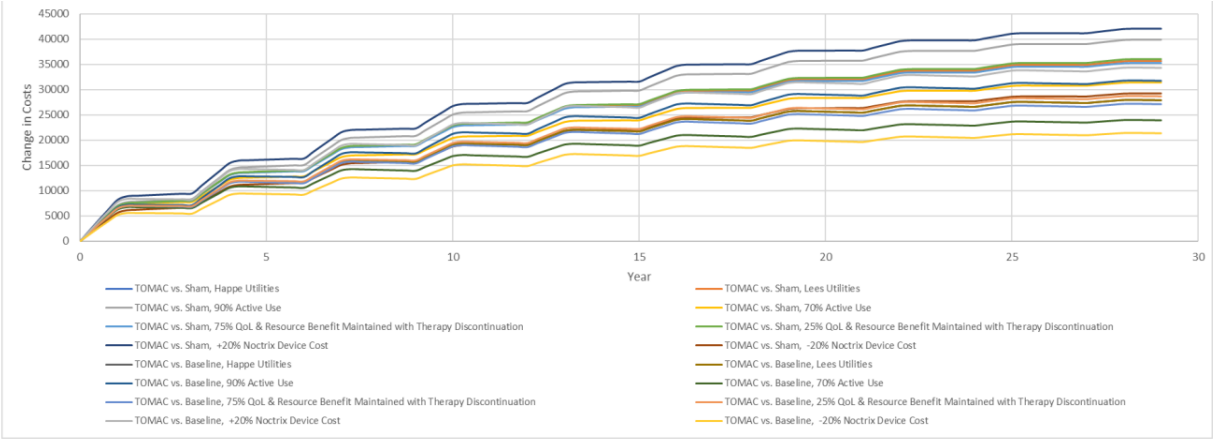
The resulting ICER over time, for scenarios exploring varied cost and utility inputs is illustrated in Figure S.6.1C above. TOMAC therapy is cost-effective under all scenarios, however under scenarios relying upon literature-sourced health event costs and/or the TOMAC vs. Baseline IRLS effect size, the resulting ICER suggests TOMAC therapy to be highly cost-effective or dominant.

Figure S.6.2A: Cumulative Change in QALYs over Time, All OWSA Scenarios



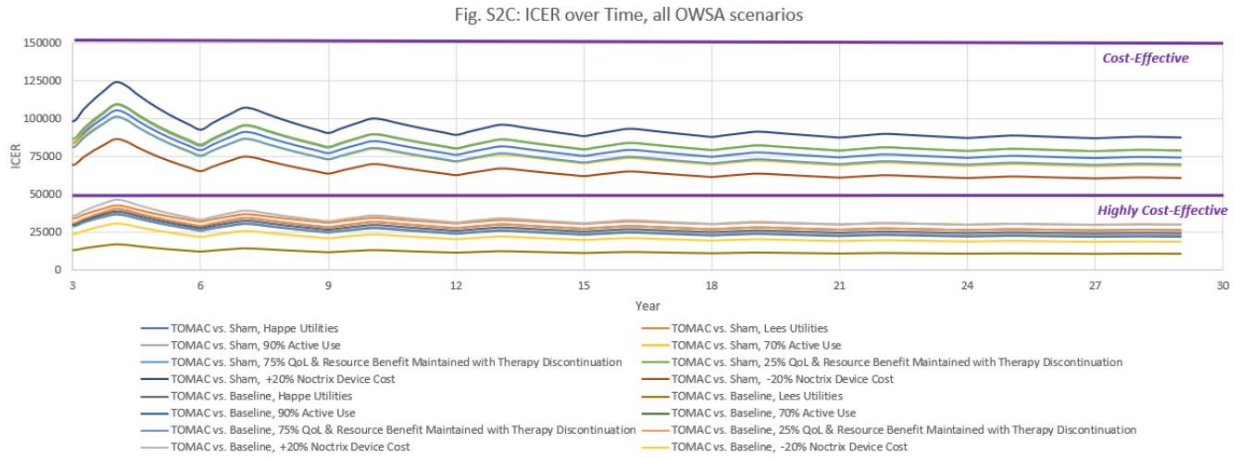
This supplemental figure includes the cumulative change in QALYs for all one-way sensitivity analyses explored. The base case still leads to the most conservative QALY projection, with only lower rates of active use and maintained QoL and resource benefits maintained following treatment discontinuation leading to lower projections. While utility estimates from Lees et al. result in the most favorable QALY projections.

Figure S.6.2B: Cumulative Change in Costs over Time, All OWSA Scenarios



This supplemental figure includes the cumulative change in costs for all one-way sensitivity analyses explored. The impact of the device cost and 13-month billing cycle on the cumulative change in cost is evident in the stepwise nature of the graph.

Figure S.6.2C: ICER over Time, All OWSA Scenarios



Supplemental Figure S2C: Change in ICER over Time, results of all one-way sensitivity analyses explored.

This supplemental figure includes the resulting ICER over time for all one-way sensitivity analyses explored. TOMAC therapy is found to be cost-effective or highly cost-effective under all scenarios explored.