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Efficacy and safety of tonic motor activation (TOMAC) for restless legs syndrome as adjunctive and monotherapy: An individual participant data systematic review and meta-analysis

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ABSTRACT

Introduction: Tonic motor activation (TOMAC) is a non-pharmacological treatment for moderate-to-severe medication-refractory Restless Legs Syndrome (RLS). This bilateral wearable device applies high-frequency electrical stimulation to the peroneal nerve, engaging the therapeutic mechanism while minimizing sleep discomfort. A recent meta-analysis evaluated TOMAC in RLS using aggregate data, which precluded subgroup analyses. The aim of our systematic review and meta-analysis was to extract individual participant data to enable the evaluation of TOMAC as adjunctive treatment and monotherapy in RLS.

Methods: This study was registered on PROSPERO (CRD420251005571). Web of Science, Scopus, and PubMed were searched, from inception to March 31, 2025, to identify studies evaluating TOMAC for RLS. Risk of bias (Cochrane Risk of Bias Tool and Downs and Black checklist) and quality of evidence (Oxford Centre for Evidence-Based Medicine 2011 guidelines) of eligible studies were assessed. Primary outcomes were changes in International RLS Study Group Rating Scale (IRLS) score for efficacy and in Medical Outcomes Study Sleep Problem Index II (MOS-II) score for sleep improvement. Main safety outcome was the incidence of device-related adverse events. Subgroup analyses evaluated TOMAC as adjunctive therapy and as monotherapy, as well as by age, RLS age-of-onset, sex, RLS severity, and stimulation amplitude.

Results: Five studies from the United States were extracted including three randomized-controlled-trials with 252 participants for analyses (69 monotherapy/183 adjunctive TOMAC therapy). Relative to sham, TOMAC significantly reduced IRLS score both as adjunctive therapy (MD: 3.39, $p = 0.0001$) and monotherapy (mean difference [MD]: 3.80, $p = 0.0047$), and significantly reduced MOS-II score both as adjunctive therapy (MD: 8.23, $p = 0.0006$) and monotherapy (MD: 9.65, $p = 0.0236$). There were no significant differences in IRLS MD based on age, age of RLS onset, sex, RLS severity, and stimulation amplitude. Mild discomfort was the only adverse event with higher prevalence for TOMAC than sham.

Conclusion: These results suggest that TOMAC is a tolerable non-pharmacological treatment that reduces RLS symptoms and improves sleep, both as adjunctive therapy and as monotherapy.

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by a well-defined set of diagnostic clinical criteria, consisting of four core components: an irresistible urge to move the legs, usually associated with uncomfortable and unpleasant sensations, which occurs during periods of rest or inactivity, primarily in the evening and night, and is relieved at least partially by movement and walking [1]. RLS symptoms can cause significant sleep disturbances with trouble falling asleep, staying asleep, and sleep deprivation often resulting in excessive daytime sleepiness and decreased daytime functioning [2]. RLS is a common disorder in the general adult population, and has a higher

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prevalence in females, in elders, and in developed countries. One recent meta-analysis study estimated a worldwide RLS prevalence at 11 % with a corrected overall pooled prevalence of RLS at 3 % [3]. Patients with RLS symptoms experience a reduced quality of life, with significant negative impact on their physical and mental health [4]. Moreover, RLS patients are at an increased risk for depression and anxiety, and impairments of memory, concentration, and productivity [5,6].

The most prescribed RLS treatments are dopaminergic agents (DAs) and alpha-2-delta ligands. Unfortunately, in long-term use of DAs, up to 70 % of RLS patients can develop augmentation [7], defined as a paradoxical aggravation in RLS symptoms while on DAs and relative to natural progression of the disorder [8,9]. In clinical trials evaluating alpha-2-delta ligands in RLS, frequent occurrence of adverse events (AEs) can lead to discontinuation of these treatments [10,11]. Compounding these pharmacological limitations, recent patient-focused qualitative research has highlighted the profound real-world barriers RLS patients face in effective self-care and sleep management, describing persistent sleep problems, subsequent daytime fatigue, and the need for guidance and consistent routines for symptom relief [12–14]. Therefore, there is a significant unmet need for effective and safe treatments for patients who suffer from moderate-to-severe RLS symptoms.

Tonic motor activation (TOMAC) is a non-pharmacological alternative treatment for RLS that has received *de novo* authorization from the US Food and Drug Administration for treatment of primary moderate-to-severe medication-refractory RLS [15]. The TOMAC system involves bilateral wearable therapeutic devices positioned over the head of the fibula bone that deliver high-frequency electrical stimulation to the peroneal nerve. The high-frequency waveform selectively activates afferent proprioceptive nerve fibers to evoke tonic, sustained muscle activation in the legs that is compatible with sleep [16]. The mechanism of TOMAC may be similar to the relief from walking and other voluntary leg movements, which also lead to leg muscle activation. TOMAC can be administered by the patient whenever symptoms present —during waking hours, at bedtime, and during sleep. Based on published evidence from randomized controlled trials (RCTs), the 2025 American Academy of Sleep Medicine (AASM) clinical practice guidelines conditionally recommended TOMAC, meaning that most adults with RLS should be offered the option of TOMAC therapy [17,18].

Various other forms of neuromodulation have been studied for the treatment of RLS, but these differ mechanistically from TOMAC and thus were not included in this systematic review [19]. These other forms of neuromodulation include implanted epidural spinal cord stimulation for patients with chronic pain and RLS [20–23], implanted deep brain stimulation for patients with essential tremor or Parkinson's disease and RLS [24–28], and other forms of non-implanted stimulation, including low-frequency (<100 Hz) or direct current stimulation [29–32]. None of these technologies had sufficient evidence to receive a recommendation in the 2025 AASM guidelines for treatment of RLS [17,18].

TOMAC delivers high frequency (4000 Hz) stimulation, which engages the therapeutic mechanism of action while minimizing uncomfortable paresthesia that could interfere with sleep. First, due to the capacitive nature of the outer layers of skin, higher frequencies result in less charge accumulation in the skin – the location of nociceptive nerve endings that signal painful sensations – and greater electric fields delivered to deeper structures including the peroneal nerve target [33,34]. As a result, higher frequencies should improve both comfort and potency, allowing delivery during sleep. Second, there is evidence that frequencies of 1000-10,000 Hz are optimal for preferentially activating afferent nerve fibers associated with TOMAC, whereas lower frequencies results in indiscriminate activation of nerve fibers, leading to irritating or uncomfortable sensations [35,36].

A recently published systematic literature review and meta-analysis evaluated the efficacy and safety of TOMAC for the treatment of RLS [37]. This report found that TOMAC was effective at improving RLS symptoms and sleep relative to sham. This prior review analyzed aggregate published data as opposed to individual participant data (IPD) and thus was unable to conduct subgroup analyses of interest, such as the response to TOMAC as monotherapy versus as adjunctive therapy to RLS medication. Additionally, the lack of IPD precluded any adjustment for relevant covariates (e.g., baseline values) or comparative subgroup analyses.

In the present systematic literature review and meta-analysis, our aim was to analyze IPD from all published studies of TOMAC to evaluate the efficacy and safety of TOMAC overall and in subgroups of interest, including adjunctive treatment versus monotherapy, medication refractory versus naïve, as well as to investigate whether there were differential treatment effects based on covariates, such as age, age of RLS onset, sex, baseline RLS severity, and stimulation amplitude.

2. Methods & materials

2.1. Protocol

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) updated 2020 guidelines [38]. The protocol and meta-analysis plan were prespecified and registered on PROSPERO (CRD420251005571) and is available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251005571.

2.2. Role of study sponsor

The study sponsor provided access to IPD from TOMAC studies but otherwise had no role in designing, conducting statistical analysis, or writing the manuscript. All work on this systematic literature review and meta-analysis was performed independently by the study authors.

2.3. Search strategy and data sources

The systematic literature search was conducted using Covidence software. Three databases were searched — Web of Science, Scopus, and PubMed — to identify studies that evaluated TOMAC (i.e., high-frequency bilateral peroneal nerve stimulation) for treatment of RLS through March 31, 2025. The search strategy consisted of “All Fields” terms related to RLS and TOMAC. The following search algorithm was employed: (“tonic motor activation” OR “TOMAC” OR “peroneal nerve stimulation” OR “noninvasive peripheral nerve stimulation” OR “nerve stimulation”) AND (“restless legs syndrome”). The time limit for retrieval was from the establishment of the database to March 31, 2025. No database filters were used to restrict studies from the search aside from the publication date. We reviewed the reference lists for articles that received a full-text review to identify additional potentially relevant studies that may have been missed. Two independent reviewers (EGK and CGB) performed title and abstract screening and full-text reviews with discrepancies adjudicated by a third reviewer (AB).

2.4. Study selection and data extraction

Studies included were based on the following eligibility criteria in hierarchical order (i.e., the first inclusion criterion not met by a study was counted as the reason for excluding that study): 1) written in English; 2) original study designed as a RCT, prospective non-RCT, cohort study, observational study, or case series; 3) adult (aged ≥18) patients treated for RLS; 4) TOMAC was an interventional treatment; 5) conference proceedings not reported in a peer-reviewed publication; 6) source RCTs with the International Restless Legs Study Group Severity Rating Scale (IRLS) as an endpoint and in which TOMAC was the only interventional treatment for assessment of efficacy; 7) source RCTs comparing the incidence of AEs between TOMAC and sham for assessment of safety; and 8) all types of studies (RCTs and non-RCTs) that assessed the incidence of device-related AEs associated with TOMAC

treatment. Studies were excluded if they were reviews, retrospective studies, opinion articles, editorials, or case reports as well as if they consisted of not original study data, and if they were conference proceedings for which a peer-reviewed publication was available.

Covidence software was used to perform data extraction which was conducted by two independent reviewers (EGK and CGB) with discrepancies resolved by a third reviewer (AB). Extracted data included study details (authors, publication year, study design, sample size, country, number of centers, patient population, medication status, duration), participant demographics (age, age of RLS onset, sex), risk of bias, quality of evidence, and baseline outcome measures. Details regarding assessment of risk of bias and quality of evidence are provided in the next section.

2.5. Quality assessment

Risk of bias for all eligible RCTs was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (ROB-2) [39]. For the eligible observational studies, risk of bias was assessed using the original 27-item Downs and Black checklist [40] with a total possible score between 0 and 28 (methodological quality of the study: excellent: 26–28, good: 20–25, fair: 15–19, and poor: ≤14 [41]) and with a 17-item modified Downs and Black checklist that evaluates items relevant to observational studies with a total possible score between 0 and 18 (low chance of bias: 12–18, average chance of bias: 6–11, high chance of bias: 0–5) [42]. One item (the same one in both the full and the modified Downs and Black checklists) is scored from 0 to 2 points while all other items are scored either 0 or 1 point. Two independent reviewers (EGK and CGB) scored risk of bias, and any disagreements were resolved through discussion with a third reviewer (AB). Quality of evidence was rated using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group's 2011 guidelines [43]. The OCEBM levels range from Level 1 (highest) to Level 4 (lowest). According to the 2011 OCEBM guidelines, only systematic reviews qualify as Level 1 evidence. RCTs and observational studies were initially graded as Level 2 and Level 3, respectively, but could be upgraded or downgraded based on bias, effect size, and/or sample size.

2.6. Outcome measures

The primary endpoint for reducing RLS symptoms was change from baseline (CFB) in IRLS total score and the primary endpoint for improving sleep was CFB in Medical Outcomes Study Sleep Problem Index II (MOS-II) score. Each of the 10 questions on the IRLS is rated from 0 to 4, and the total score (range, 0–40) provides an overall assessment of RLS severity with higher scores indicating greater severity [44]. The minimal clinically important difference (MCID) for the IRLS is 3.0 points [17,45]. The MOS Sleep Scale-R consists of 12 items measuring subjective experiences of sleep across six domains [46]. MOS-II is calculated using 9 of the 12 MOS Sleep Scale-R items and provides an overall summary of sleep problems [46]. Medical Outcomes Study Sleep Problem Index I (MOS-I), calculated from 6 of the 12 items of the MOS Sleep Scale-R, is a global summary of sleep quality [46]. Both indices are scored on a 0–100 scale, with higher scores indicating more severe sleep problems [46] with a standardized mean difference exceeding −0.2 indicating a clinically significant improvement in sleep quality [17]. The Patient Global Impression of Improvement (PGI-I) is a 7-point, single-item scale used to assess the patient's perception of RLS improvement or worsening where 1 = very much improved, 2 = much improved, 3 = a little improved, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse [47]. The secondary endpoint for reducing RLS symptoms was PGI-I responder rate, defined as percentage of participants with PGI-I score of 1 or 2; the MCID is 15 % [17]. The secondary endpoint for improving sleep was CFB in the MOS-I score. For safety analysis, adverse events (AEs) were categorized by system organ class and preferred terms based on Medical Dictionary for Regulatory Activities (MedDRA) version 3.0 definitions, then categorized by severity.

2.7. Subgroups analyses and covariates

Based on IPD and using the same definitions applied across source studies, participants were categorized as adjunctive or non-adjunctive/monotherapy and refractory or naïve. Participants were categorized as refractory if they were taking or had discontinued RLS medication at study entry or naïve if they had not taken RLS medication before study entry. Participants were defined as adjunctive if they were taking prescription medication for RLS at study entry and as monotherapy if not. Monotherapy (non-adjunctive) included a mix of both patients who had never taken RLS medication (naïve) and patients who had stopped taking RLS medication (refractory). Efficacy of TOMAC versus sham was also examined by patient characteristics (age, age of RLS onset, sex, and baseline IRLS score) and maximum programmed stimulation intensity (TOMAC can be programmed within a range of 15–40 mA [mA]).

2.8. Data synthesis and statistical analyses

Data analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC). Study authors provided IPD for each of the included studies and IPD was used for all statistical meta-analysis. The pooled intent-to-treat (ITT) analysis set included all participants who enrolled and were randomized across any of the source RCTs; this population was utilized for all analyses comparing efficacy, sleep quality, and AEs between TOMAC and sham. The pooled safety analysis set for assessing device-related AEs included all participants who received TOMAC in any of the studies eligible for analysis of safety.

Data were generally complete, and thus the primary analyses excluded the small number of participants with missing data. All p-values less than 0.05 were considered statistically significant.

The approaches to all analyses for all participants (as well as subgroups) were pre-specified. All efficacy analyses were conducted using a two-step approach. First, a generalized linear model (GLM) was implemented to analyze each study independently and heterogeneity of results across studies was assessed with Cochrane's Q and the I^2 statistic. A Chi-square test based on Cochrane's Q was also conducted, and heterogeneity of results was pre-specified to be observed if the Chi-square p-value was <0.05 or if the I^2 statistic was >50 %. In the presence of heterogeneity, a generalized linear mixed model (GLMM) was implemented to analyze pooled results that adjusted for the baseline score as a covariate and for source RCT and participant nested within source RCT as random effects. Otherwise, a GLM that adjusted for the baseline score was used to analyze the pooled results as a single study.

Efficacy and sleep quality endpoints were also analyzed among the following subgroups: 1) TOMAC monotherapy (no adjunctive prescription medication for RLS), 2) TOMAC as adjunctive therapy, 3) medication-naïve patients (TOMAC monotherapy and no prior history of prescription medication for RLS), and 4) medication-refractory patients as defined in each of the studies. Multiplicity was accounted for with respect to the TOMAC monotherapy subgroup by using a fixed sequence testing strategy, in which the efficacy and sleep endpoints were tested hierarchically in the following order: 1) CFB in IRLS, 2) CFB in MOS-II, 3) PGI-I responder rate, and 4) and CFB in MOS-I. Analyses for each of the above subgroups paralleled the primary analysis approach for each of the efficacy endpoints.

Comparative subgroup analyses were also performed for continuous covariates (age, age of RLS onset, baseline IRLS score, maximum programmed stimulation intensity [mA, applied to either leg]) and for one additional categorical covariate (sex). These subgroups were analyzed using similar models to the overall analyses with additional independent variables for the subgroup and its interaction (treatment*subgroup). Estimates and 95 % confidence intervals (CIs) for the treatment effect were prepared for all patients, and for each subgroup level including

TOMAC monotherapy, and TOMAC as adjunctive therapy and will be presented in forest plots, along with the p-value for the interaction term which tests for a differential treatment effect between levels of the relevant subgroup.

3. Results

The PRISMA flow diagram of the study selection process is shown in Fig. 1. The literature search identified 699 studies, of which 75 duplicates were removed. The remaining 624 studies were eligible for title and abstract screening, of which 608 were excluded. Sixteen studies were deemed suitable for full-text evaluation. Five of the 16 studies that received a full-text evaluation were selected for the final analyses in this study including three RCTs [48–50] (all included in the subsequent meta-analysis), one prospective, open-label, single-arm clinical trial [51], and one extension study [52]. No additional articles were identified by manual screening of the references of the studies included.

3.1. Summary of included studies

Table 1 summarizes the characteristics of the five included studies. All studies were multicenter and conducted in the US. Due to the crossover design of Buchfuhrer et al. (2021) [37,50] participants contributed data for both TOMAC and sham; these were treated as separate samples, yielding total sample size of 252 for efficacy and for safety comparisons between TOMAC and sham (all participants across all three RCTs), and 155 for device-related adverse events (all TOMAC treated participants across all five studies).

The efficacy analysis included three RCTs: Bogan et al. [48], Singh et al. [49], and Buchfuhrer et al. (2021) [50]. Of the 252 participants in the efficacy population, 69 were medication free at study entry (non-adjunctive) and 183 had taken RLS medication at study entry (adjunctive); no changes to medication were permitted during any of the studies. As shown in Table 1, across the RCTs, baseline characteristics and demographics were similar; mean age ranged from 55.7 to 57.5 years, percent female ranged from 54 % to 67 %, mean baseline IRLS score ranged from 23.4 to 25.9 points (across all study arms), and mean baseline MOS-II score ranged from 43.2 to 52.4 points (across all study arms).

Non-pooled efficacy results for each study are summarized in Supplementary Table S1. Whereas Roy et al. [52] previously reported changes from RESTFUL study [48] entry, we reported changes from the extension study entry – at which time participants who had been previously on TOMAC treatment (n = 103) were instructed to either continue TOMAC ("TOMAC", n = 44) or cease TOMAC ("Control", n = 59). Analyzed in this manner, mean difference (MD) in IRLS change was −7.3 points (TOMAC: 4.0, Control: +3.4), difference in PGI-I responder rate was +51 % (TOMAC: +7 %, Control: 44 %), MD in MOS-II change was −12.1 points (TOMAC: 1.6, Control: +10.5) and MD in MOS-I change was −11.0 points (TOMAC: 1.6, Control: +9.4).

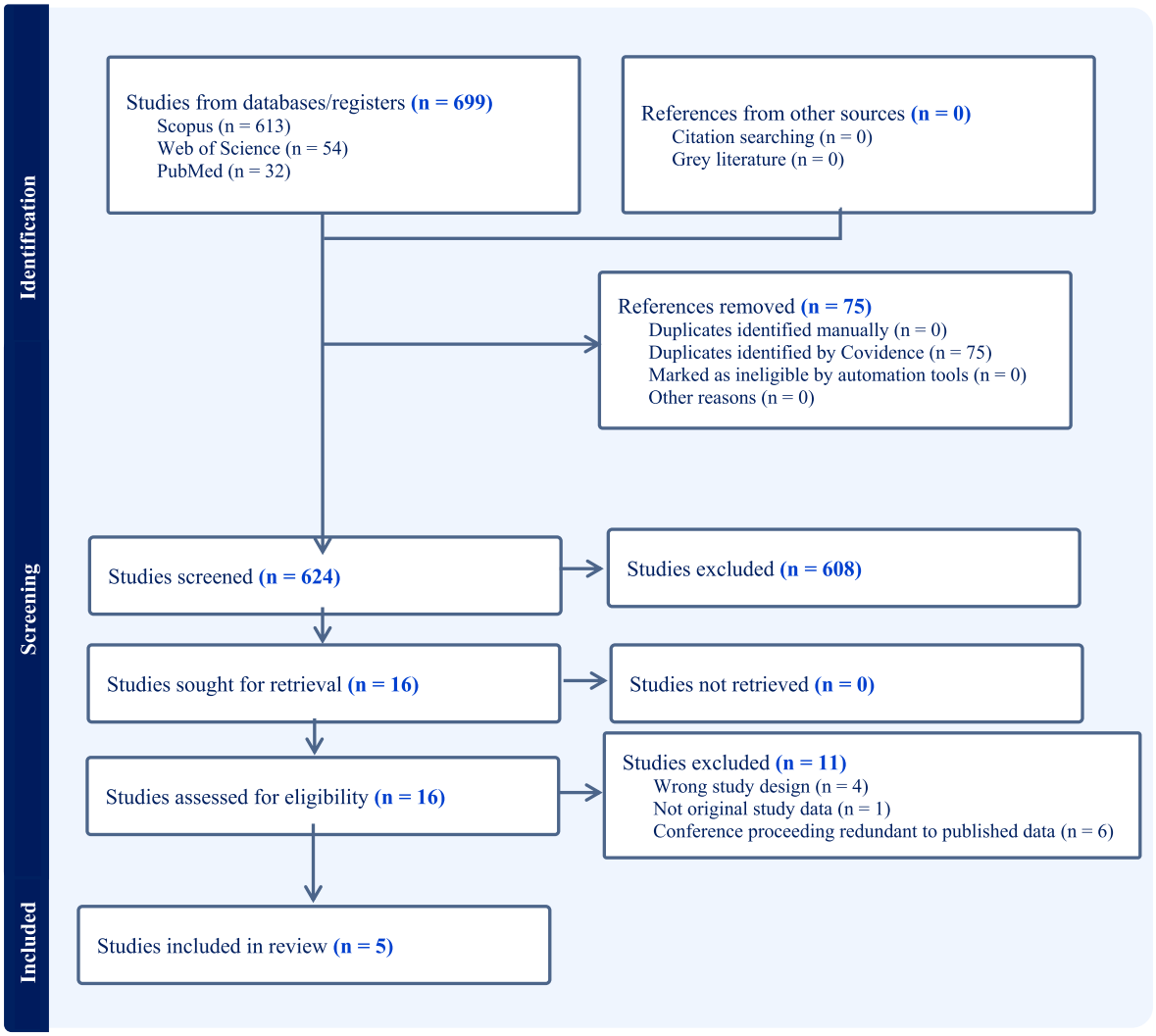

Fig. 1. Flowchart of studies included in the meta-analysis.

Table 1
Summary of characteristics for all included studies.

Source	Study Design	ITT Sample Size (n)	Quality of Evidence	Risk of Bias	Patient Population	Medication Status: n	Age (years)[g]	Sex (% female)	Duration (weeks)	Baseline IRLS[g]	Baseline MOS-II[g]	Baseline MOS-I[g]
Buchfuhrer et al. (2021) [50]	RCT Crossover SB	Total: 37 TOMAC: 37 Sham: 37	3	Some concerns[a]	Moderate-severe RLS	Refractory: 23 (46[h]) Naive: 14 (28[h]) Adjunctive: 22 (44[h]) Non-adjunctive[d]: 15 (30[h])	55.7 ± 12.4	54 %	2	24.1 ± 4.0	Not applicable	Not applicable
Bogan et al. (2023) [48]	RCT Parallel DB	Total: 133 TOMAC: 68 Sham: 65	2	Low[a]	Moderate-severe RLS & refractory	Refractory: 133 Naive: 0 Adjunctive 119 Non-adjunctive 14	57.5 ± 11.4	60 %	4 Endpoints assessed at 4-wks, 8-wk total duration including extension	T: 25.2 ± 5.3 C: 25.4 ± 5.3	T: 52.4 ± 17.6 C: 48.1 ± 18.3	T: 48.1 ± 17.2 C: 44.4 ± 17.7
Singh et al. (2024) [49]	RCT Parallel SB	Total: 45 TOMAC: 22 Sham: 23	2	Some concerns[a]	Moderate-severe RLS	Refractory: 25 Naive: 20 Adjunctive 20 Non-adjunctive 25	56.1 ± 12.2	67 %	2	T: 25.9 ± 4.5 C: 23.4 ± 4.6	T: 52.1 ± 16.6 C: 43.2 ± 11.3	T: 48.8 ± 17.3 C: 41.7 ± 12.7
Roy et al. (2023) [52]	Prospective Parallel OL extension	Total: 103 TOMAC: 44 Standard of care: 59	2	Low chance of bias (16/18)[b] Good quality (21/28)[c]	Moderate-severe RLS and refractory (upon entry to parent study)	Refractory: 103 Naive: 0 Adjunctive 87 Non-adjunctive 16	57.6 ± 11.7	56 %	24 Endpoints assessed at 24-wks, 32-wk total duration including cessation period	T: 17.1 ± 6.8[f] C: 17.0 ± 7.6[f]	T: 29.1 ± 14.1[f] C: 35.9 ± 18.0[f]	T: 27.0 ± 13.9[f] C: 33.7 ± 17.9[f]
Buchfuhrer et al. (2023) [51]	Prospective Single-arm OL	Total: 20 TOMAC: 20	4	Low chance of bias (12/18)[b] Fair quality (18/28)[c]	Opioid-treated RLS	Adjunctive: 20	62.9 ± 10.2	40 %	≤9	T: 9.8 ± 8.5	Not applicable	Not applicable

Abbreviations: C, control; DB, double blind, IRLS, International RLS Study Group Rating Scale; Intent to treat, ITT; MOS-II, Medical Outcomes Study Sleep Problem Index II; Medical Outcomes Study Sleep Problem Index I; OL, open label; OLE, open label extension; RCT, randomized controlled trial; RLS, restless legs syndrome; SB, single blind; SD, standard deviation; SOC, standard of care; TOMAC, tonic motor activation; T, TOMAC; Wk, week. Note. See Methods for definitions of refractory, naïve, adjunctive, and non-adjunctive subgroups.

[f]Baseline for Roy et al. refers to the end of the RESTFUL study (after at least 4-weeks of TOMAC treatment) and beginning of the 24-week extension.

[g]Value is mean ± standard deviation.

[h]There are two data points per participant in Buchfuhrer et al. (2021) due to crossover design. The number of data points is listed in parentheses, for example 23 (46) means 23 participants and 46 data points.

[e]Duration of endpoint measurement.

[a] Based on RoB2 [39].

[b] Based on modified Downs & Black [42].

[c] Based on original Downs & Black [40].

[d] Monotherapy (non-adjunctive) includes a mix of both patients who had never taken RLS medication (naïve) and patients who had stopped taking RLS medication.

3.2. Quality assessment

Among the three RCTs evaluated with the RoB 2 tool (Supplementary Fig. S1), Bogan et al. [48] had low risk of bias in all domains and low risk of overall bias, Singh et al. [49] had some concerns of bias in the randomization domain and thus some concerns of overall bias, and Buchfuhrer et al., 2021 [50] had some concerns of bias in both the randomization and missing outcomes domains and thus some concerns of overall bias. In OCEBM quality of evidence grading, Buchfuhrer et al., 2021 [50] was downgraded to Level 3 due to some concerns of bias in multiple domains and the other two RCTs [48,49] were graded as Level 2. As shown in Table 1, among the two observational studies evaluated with the Downs & Black (and modified Downs & Black), Roy et al. [52] had low chance of bias (and good quality) and Buchfuhrer et al., 2023 [51] had low chance of bias (and fair quality). In OCEBM quality of evidence grading, Roy et al. [52] was upgraded to level 2 primarily due to the large effect size of a 7.3 point improvement in the IRLS score for TOMAC relative to control (supplemetary Table S1) and secondarily due to the fairly large sample size and low risk of bias. Buchfuhrer et al., 2023 [51] was downgraded to level 4 based on the fair quality and small sample size.

3.3. Efficacy of TOMAC

All efficacy results were based on pooling IPD from the selected three RCTs [48–50] (Table 2) as there was no evidence of heterogeneity for any endpoint either overall or within-subgroup ($p > 0.30$ and $I^2<50$ % for all).

3.3.1. Primary outcomes

The pooled mean difference (MD) in IRLS change from baseline for TOMAC relative to sham was −3.50 points (n = 242), indicating a statistically significant improvement in RLS severity (95 % CI: 4.91 to −2.09; $p < 0.001$). The pooled MD in MOS-II change from baseline was −8.50 points (n = 171), indicating statistically significant improvement in sleep quality (95 % CI: 12.51 to −4.49; $p < 0.001$). Forest plots for primary endpoints (IRLS and MOS-II) are shown in Fig. 2.

3.3.2. Secondary outcomes

For the secondary endpoint for RLS improvement – PGI-I responder rate – the pooled difference in responder rate ("risk difference") between TOMAC and sham was 36 % (n = 229), which was statistically significant (95 % CI: 25 %–48 %; $p < 0.001$). For the secondary endpoint for sleep improvement (MOS-I), the pooled MD was −7.91 (n = 171), which was also statistically significant (95 % CI: 11.89 to −3.92; $p < 0.001$). Forest plots for secondary endpoints (PGI-I and MOS-I) are shown in supplemetary Fig. S2.

3.3.3. Sensitivity analyses

Next, we tested if the primary outcomes remained similar if we only included the higher-quality RCTs in the analysis. As noted previously, two of the included RCTs were graded Level 2 evidence and one was Level 3 evidence. When including only the Level 2 studies (n = 171) [48, 49], the MD in IRLS CFB was −3.51 points (95 % CI: 5.18 to −1.83; p = 0.0001) compared to −3.50 points with all three studies included. The Level 3 study did not assess MOS, so the results for MOS-II were the same as described above. In summary, the results were robust both when including or excluding the Level 3 RCT [50].

3.3.4. Medication status subgroups analyses

The primary and secondary analyses above were repeated independently for the subgroups of patients with no adjunctive medication (monotherapy, n = 69) and patients with adjunctive medication (adjunctive, n = 183). All endpoints were statistically significant for both of these subgroups (Table 2). MD in IRLS was −3.80 points for monotherapy subgroup (95 % CI: 6.39 to −1.21, p = 0.0047) and −3.39

Table 2
Meta-analysis of efficacy overall and for subgroups defined by medication status based on included randomized controlled trials.

Population/ Subgroup	IRLS CFB	PGI-I responder rate	MOS-II CFB	MOS-I CFB
All participants	MD: 3.50, p < 0.001 95 % CI: 4.91, −2.09 n = 242 Q = 0.204 (p = 0.903) $I^2 = 0$	RD: 36 %, p < 0.001 95 % CI: 25 %, 48 % n = 229 Q = 1.519 (p = 0.468) $I^2 = 0$	MD: 8.50, p < 0.001 95 % CI: 12.51, −4.49 n = 171 Q = 0.150 (p = 0.699) $I^2 = 0$ SMD: 0.726 95 % CI: 1.028, −0.424	MD: 7.91, p < 0.001 95 % CI: 11.89, −3.92 n = 171 Q = 0.129 (p = 0.720) $I^2 = 0$ SMD: 0.676 95 % CI: 0.978, −0.374
TOMAC monotherapy	MD: 3.80, p = 0.005 95 % CI: 6.39, −1.21 n = 65 Q = 0.163 (p = 0.922) $I^2 = 0$	RD: 42 %, p < 0.001 95 % CI: 21 %, 63 % n = 63 Q = 0.718 (p = 0.698) $I^2 = 0$	MD: 9.65, p = 0.024 95 % CI: 17.92, −1.38 n = 37 Q = 0.28 (p = 0.867) $I^2 = 0$ SMD: 0.795 95 % CI: 1.463, −0.127	MD: 9.14, p = 0.043 95 % CI: 17.98, −0.31 n = 37 Q = 0.013 (p = 0.909) $I^2 = 0$ SMD: 0.707 95 % CI: 1.375, −0.040
TOMAC as adjunctive therapy	MD: 3.39, p < 0.001 95 % CI: 5.09, −1.70 n = 177 Q = 0.711 (p = 0.701) $I^2 = 0$	RD: 34 %, p < 0.001 95 % CI: 20 %, 47 % n = 166 Q = 3.488 (p = 0.175) I^2 = 42.7 %	MD: 8.23, p < 0.001 95 % CI: 12.88, −3.59 n = 134 Q = 0.183 (p = 0.669) $I^2 = 0$ SMD: 0.701 95 % CI: 1.043, −0.360	MD: 7.63, p = 0.001 95 % CI: 12.15, −3.11 n = 134 Q = 0.334 (p = 0.557) $I^2 = 0$ SMD: 0.662 95 % CI: 1.004, −0.320
Medication naïve	MD: 4.13, p = 0.001 95 % CI: 7.21, −1.05 n = 43 Q = 0.093 (p = 0.761) $I^2 = 0$	RD: 41 %, p = 0.005 95 % CI: 13 %, 68 % n = 41 Q = 0.845 (p = 0.655) $I^2 = 0$	MD: 5.69, p = 0.268 95 % CI: 16.04, 4.66 n = 19 Q = N/A, I^2=N/A SMD: 0.558 95 % CI: 1.528, 0.411	MD: 4.11, p = 0.402 95 % CI: 14.24, 6.01 n = 19 Q = N/A, I^2=N/A SMD: 0.365 95 % CI: 1.335, 0.604
Medication refractory	MD: 3.40, p < 0.001 95 % CI: 5.00,-1.79, n = 198 Q = 0.614 (p = 0.736) $I^2 = 0$	RD: 35 %, p < 0.001 95 % CI: 22 %, 48 %, n = 188 Q = 2.387 (p = 3031) I^2 = 16.2 %	MD: 8.87, p < 0.001 95 % CI: 13.25,-4.49, n = 152 Q = 0.425 (p = 0.514) $I^2 = 0$ SMD: 0.741 95 % CI: 1.062,-0.421	MD: 8.46, p < 0.001 95 % CI: 12.80, −4.11 n = 152 Q = 0.741 (p = 0.389) $I^2 = 0$ SMD: 0.708 95 % CI: 1.029, −0.388

Abbreviations: CFB, change from baseline; CI, confidence interval; IRLS, International RLS Study Group Rating Scale; MD, mean difference; MOS-II, Medical Outcomes Study Sleep Problem Index II; MOS-I, Medical Outcomes Study Sleep Problem Index I; Patient Global Impression of Improvement, PGI-I; RD, risk difference; SMD, standardized mean difference; TOMAC, tonic motor activation.

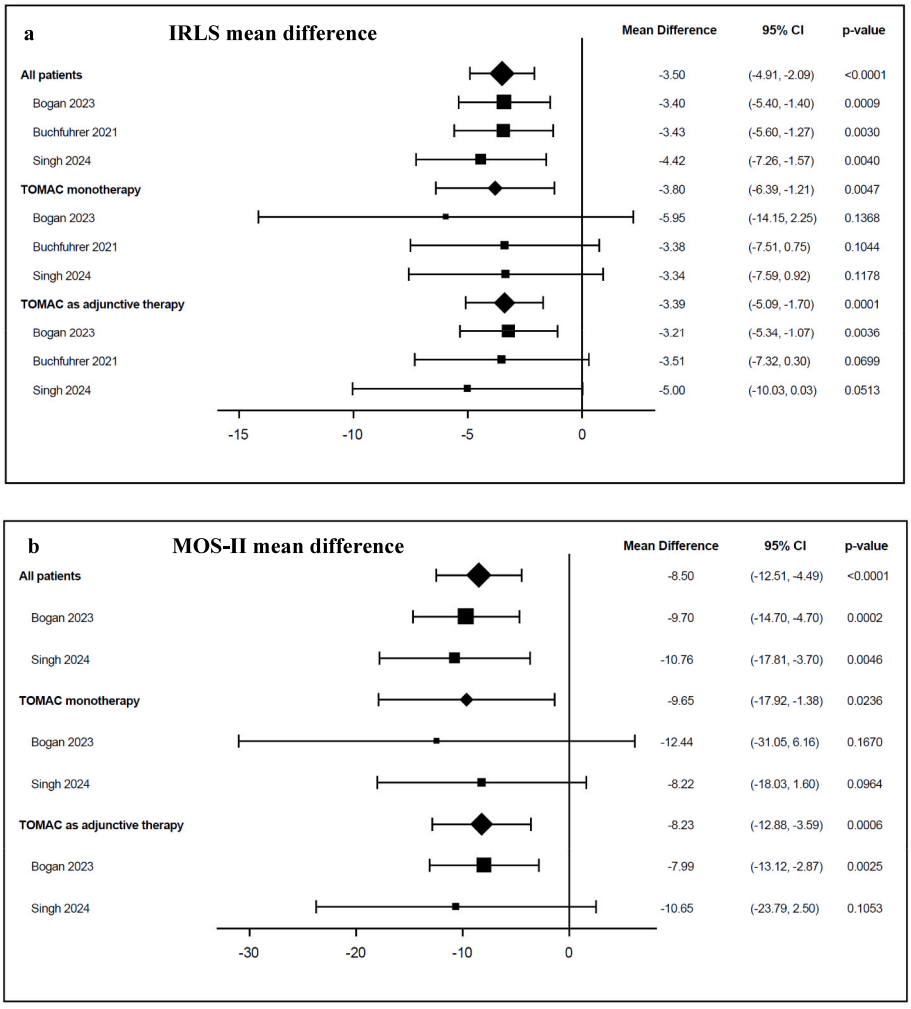

Fig. 2. Forest plots for primary outcomes

Forest plots for (a) the International Restless Legs Study Group Severity Rating Scale (IRLS) mean difference, and (b) Medical Outcomes Study Sleep Problem Index II (MOS-II) mean difference, For each, analysis was conducted separately for all patients, patients with TOMAC monotherapy, and patients with TOMAC as adjunctive therapy. Each individual study is represented as a rectangle and overall pooled effects are represented by a diamond. Size of squares/diamonds are proportional to sample size. Horizontal lines represent 95 % confidence intervals.

for the adjunctive subgroup (95 % CI: 5.09 to −1.70, p = 0.0001), indicating a statistically significant improvement favoring TOMAC for both subgroups. MD in MOS-II was −9.65 (95 % CI: 17.92 to −1.38; p = 0.024) for the monotherapy group and −8.23 (95 % CI: 12.88 to −3.59; p = 0.0006) for the adjunctive group. The risk difference (RD) in PGI-I responder rate was 42 % (95 % CI: 21 %–63 %; p < 0.001) for the monotherapy group and 34 % (95 % CI: 20 %–47 %; p < 0.001) for the adjunctive group. The analyses were also repeated for the subgroups of medication-naïve (n = 48) and medication-refractory (n = 204) participants. The difference between this analysis and the adjunctive analysis above was that 21 medication-refractory patients had no adjunctive medication due to cessation of failed RLS medication. For medication-refractory participants, TOMAC significantly improved all outcome measures relative to sham (Table 2). For medication-naïve patients, TOMAC significantly improved both RLS outcome measures (IRLS and PGI-I), but was underpowered to detect improvement in sleep quality as only one RCT assessed MOS in 19 medication-naïve patients.

Next, we compared the results above to the recommended MCID of 3 points on the IRLS [15,45]% on the PGI-I responder rate, and −0.2 for the MOS-II and MOS-I employed in the 2025 AASM Clinical Practice Guidelines [17]. For all subgroups above, IRLS MDs ranged from −3.39 to −4.13 points, all of which exceeded the MCID of −3.0 points. Across subgroups, PGI-I responder rate RDs ranged from 35 % to 42 %, all of which exceeded the MCID of 15 %. Across subgroups, the standardized mean differences (SMDs) for MOS-II ranged from −0.558 to −0.795 and, for MOS-I, ranged from −0.365 to −0.708 (Table 2), all of which exceeded the MCID of −0.2.

3.3.5. *Covariate analyses*

Table 3 shows the meta-analysis results for comparative subgroups. For the clinically relevant covariates of age, age of RLS onset, and baseline RLS severity (as measured by the IRLS score at study entry), which was analyzed both as a continuous variable (p = 0.796) and as a categorical variable (p = 0.733; moderate, n = 48; severe, n = 162; very severe, n = 32), there was no evidence of a differential treatment effect (p > 0.10 for all comparisons, Table 3). Interestingly, higher baseline IRLS score was associated with larger IRLS improvement across all participants (p = 0.0061) and in both the TOMAC and sham groups.

There were no significant differences by sex on IRLS, PGI-I score, MOS-II CFB, and MOS-I CFB (p > 0.10 for all). However, relative to males, females had a statistically significant larger difference in PGI-I responder rate (RD = 32 %; p = 0.0067) and a trend towards a larger improvement in RLS severity (IRLS MD = −2.72; p = 0.0646) for TOMAC compared to sham. To evaluate if this trend was meaningful, we compared male and female TOMAC responses at the end of the open-label extension phase of Bogan et al. [48] and found that there was no

Table 3
Meta-analysis of efficacy by patient characteristics and stimulation intensity.

	IRLS CFB	PGI-I score	PGI-I responder rate	MOS-II CFB	MOS-I CFB
Pooled analysis across all three RCTs					
Age	dSlope: +0.05440 SE: 0.06038 p = 0.369	dSlope: 0.008672 SE: 0.01083 p = 0.424	dSlope: 0.00356 SE: 0.004882 p = 0.467	dSlope: 0.2276 SE: 0.1740 p = 0.193	dSlope: 0.2796 SE: 0.1732 p = 0.109
Sex	MD: 2.7273 SE: 1.4689 p = 0.065	MD: 0.3729 SE: 0.2618 p = 0.156	RD: 31.96 % SE: 11.68 % p = 0.007	MD: 5.2228 SE: 4.0688 p = 0.201	MD: 4.4629 SE: 4.0733 p = 0.275
Age of RLS onset	dSlope: 0.01099 SE: 0.04244 p = 0.796	dSlope: 0.004009 SE: 0.007556 p = 0.596	dSlope: 0.00200 SE: 0.003390 p = 0.557	dSlope: 0.04298 SE: 0.1214 p = 0.724	dSlope: 0.09176 SE: 0.1210 p = 0.449
Stimulation intensity (mA)	dSlope: 0.02377 SE: 0.1133 p = 0.834	dSlope: 0.01423 SE: 0.02048 p = 0.488	dSlope: 0.00782 SE: 0.009241 p = 0.398	dSlope: 0.7565 SE: 0.3179 p = 0.019	dSlope: 0.8015 SE: 0.3161 p = 0.012
Baseline IRLS score	dSlope: 0.05015 SE: 0.1469 p = 0.733	dSlope: 0.03722 SE: 0.02623 p = 0.157	dSlope: 0.01433 SE: 0.01184 p = 0.228	dSlope: 0.3409 SE: 0.3915 p = 0.385	dSlope: 0.3049 SE: 0.3890 p = 0.434
Analysis of sex differences in the TOMAC-only extension phase of Bogan et al. (2023)					
Female	Mean: 7.79	Mean: 2.28	61.3 %	Mean: 15.45	Mean: 13.04
Male	Mean: 7.96	Mean: 2.36	60.0 %	Mean: 13.81	Mean: 12.52
P value	p = 0.8865	p = 0.6715	p = 0.8808	p = 0.5513	p = 0.8443

Note: Difference in slope (dSlope) estimates were calculated for continuous variables, and the mean difference (MD) and risk difference (RD) estimates were calculated for categorical variables. Stimulation intensity was assessed as the maximum applied to either leg.
Abbreviations: CFB, change from baseline; IRLS, International RLS Study Group Rating Scale; mA, milliampere; MD, mean difference; MOS-II, Medical Outcomes Study Sleep Problem Index II; MOS-I, Medical Outcomes Study Sleep Problem Index I; Patient Global Impression of Improvement, PGI-I; RCTs, randomized controlled trials; RD, risk difference; SE, standard error; TOMAC, tonic motor activation.

evidence of even a weak trend towards a sex difference in any of the outcome measures ($p > 0.50$ for all, Table 3).

The TOMAC device can be programmed within a range of 15–40 mA; patients programmed to higher maximum stimulation intensities had no difference in RLS outcome measures (IRLS, PGI-I) but had less improvement in sleep (MOS-II, MOS-I). Interestingly, this trend was due to less improvement in the subgroup of participants with maximum intensities between 35 and 40 mA (n = 62), there was no such effect for patients with maximum intensities between 15 and 34 mA (n = 189) for either MOS-II ($p = 0.4539$) or MOS-I ($p = 0.3781$).

3.4. Safety of TOMAC

The pooled results for adverse events (AEs) are summarized in Supplementary Table S2. Only two MedDRA preferred terms, mild discomfort and mild skin irritation, were reported by more than 5 % of participants assigned to TOMAC. Mild discomfort (at the device application site) was more prevalent with TOMAC than sham (25.8 % vs. 12.8 %, $p = 0.0089$). In contrast, mild skin irritation (at the device application site) was equally prevalent with TOMAC and sham (5.5 % vs. 7.2 %, $p = 0.5734$). No other preferred terms were significantly more common during TOMAC compared to sham. AE-related dropout rates were low for both TOMAC and sham groups, but the dropout rate was higher for TOMAC than sham (3.9 % vs. 0 %, $p = 0.0256$). There was no difference in the rate of moderate ($p = 0.3280$), severe ($p = 0.3240$), or serious ($p = 0.3240$) AEs between TOMAC and sham. AEs were categorized in each study based on relationship to device usage as opposed to other medical factors; pooling data on device-related AEs across all five studies resulted in similar frequencies of discomfort (29.0 %) and skin irritation (4.5 %).

4. Discussion

This systematic review and meta-analysis demonstrated the efficacy and safety of TOMAC for reducing RLS severity and improving sleep quality in patients with moderate-severe RLS. Improvement in RLS severity (IRLS score) was significantly higher for TOMAC versus sham and exceeded the MCID of 3.0 points [45]. Improvement in MOS-II, MOS-I, and PGI-I responder rate were also statistically significant and exceeded the clinically significant difference thresholds proposed by the 2025 AASM Clinical Practice Guidelines (SMD of 0.2 for MOS and 15 % responder rate difference for PGI-I) [17]. The IRLS improvement of 3.5 points for TOMAC relative to sham exceeded the MCID (3.0 points) but was lower than improvements reported in meta-analyses of dopamine agonists [53] and alpha-2-delta ligands [54], which ranged from 4.6 to 5.3 points. Conversely, the tolerability of TOMAC was favorable relative to these drugs [53–55].

Safety analysis indicated that TOMAC-related AEs were limited to a higher rate of mild discomfort. Prior work has noted that this discomfort is typically limited to the application site and resolves rapidly after adjusting intensity or positioning [48]. These results replicate and confirm many of the findings from a prior publication that used aggregate data instead of IPD [37]. A small percentage of these mild AEs likely contributed to treatment discontinuation, which was higher for TOMAC than sham (3.9 % vs. 0 %, $p = 0.0256$). These may primarily occur early in TOMAC treatment; in the 24-week extension study to the RESTFUL RCT [52], there were no treatment discontinuations due to an AE. Together, the findings from both meta-analyses provide strong evidence that TOMAC is effective and safe in people with moderate-to-severe RLS.

Our subgroup analyses demonstrate that TOMAC is similarly effective regardless of RLS medication status. Using pooled IPD, we were able to show that TOMAC reduces RLS severity and improves sleep regardless of whether it is administered as monotherapy or as adjunctive to medication. Efficacy as monotherapy is relevant for patients seeking an alternative to medication and could be relevant to special adult populations with RLS, such as patients with end-stage renal disease or during pregnancy as well as pediatric RLS. Efficacy as adjunctive is relevant for patients who are unable to stop using adjunctive medication due to augmentation or severe RLS. The IPD approach allowed sufficient statistical power to determine – for the first time – that TOMAC monotherapy significantly improved MOS-II and MOS-I compared to sham, thereby demonstrating sleep improvement.

The IPD approach enabled novel covariate analyses demonstrating that TOMAC is similarly effective in reducing RLS severity across people with different baseline characteristics, including age, age of RLS onset, sex, baseline RLS severity, and TOMAC stimulation intensity. Most notably, TOMAC was equally effective in participants with moderate, severe, and very severe baseline RLS severity. Consistent with typical RLS trial design, participants with mild RLS were not included in any of the RCTs. Comparing TOMAC versus sham in RCTs, females had larger PGI-I responder rate than males. However, comparison of male and female TOMAC responses at the end of the open-label extension phase of Bogan et al. [48] revealed no evidence of even a weak trend towards a sex difference in any of the outcome measures, suggesting that response

to open-label TOMAC is similar regardless of sex. These results could be explained by a stronger placebo effect among males, as has been previously reported as opposed to a difference in response to TOMAC [56,57]. Alternatively, it might take slightly longer for men to experience therapeutic benefits than women, since men tend to have higher electrical stimulation thresholds for sensory and motor activation than women, explaining why men 'catch up' to women during the extension period [58]. Participants titrated to higher TOMAC intensities (35–40 mA) had less improvement in sleep than those using lower intensities (15–34 mA), but no difference in RLS improvement (Table 3); this could indicate that these participants may have been programmed to higher-than-optimal intensities or that they should be instructed to use lower intensities during sleep.

Results of our meta-analysis suggest that TOMAC reduces RLS symptoms regardless of medication history, similar to the nearly universal relief from walking and other voluntary leg movements. It is not yet fully understood why either modality of leg muscle activation – TOMAC or walking – leads to reduction in RLS symptoms. One theory is that primary RLS is caused by blockage of ascending pathological signals at the spinal cord level [16,59]. Notably, spinal excitability is elevated in RLS patients during the symptomatic phase and can be modulated by neurostimulation. Previous studies showed increased Hoffmann Reflex H2/H1 responses after double H-reflex stimulation, pointing to an increased spinal excitability in RLS patients during their symptomatic phase [30,60]. Application of anodal transcutaneous spinal direct current stimulation led to a reduction of H2/H1 responses (interstimulus intervals of 200 and 300 ms), indicating a decrease in spinal excitability. It is possible that increased RLS spinal excitability could be advantageous for TOMAC, by allowing muscle activation with lower stimulation intensity levels that are more comfortable and thus compatible with sleep. This would be consistent with the recommended usage of TOMAC after symptoms start as opposed to prior to symptom onset.

The pooled safety IPD demonstrated the benign safety and tolerability profile of TOMAC. Only mild discomfort and mild skin irritation were reported by more than 5 % of participants assigned to TOMAC. A higher prevalence of mild discomfort (at the device application site) was seen with TOMAC versus sham, suggesting it may be due to electrical stimulation. In contrast, mild skin irritation (at the device application site) was equally prevalent with TOMAC and sham, suggesting it may be due to device materials. There was no difference in the rate of moderate, severe, or serious AEs between TOMAC and sham, and AE-related dropout rates were low for both groups. Pooling data on device-related AEs across all five studies resulted in similar frequencies of discomfort (29.0 %) and skin irritation (4.5 %), further suggesting that these AEs are likely related to TOMAC usage as opposed to other factors.

This meta-analysis had several limitations including limited generalizability and lack of independent replication. The generalizability of the meta-analysis results is limited by the patient population enrolled in the TOMAC RCTs, which included only US adults with moderate-to-severe RLS, thereby restricting the applicability of the findings to regional, world, and diverse populations. Additionally, the reliance on industry-sponsored studies potentially introduced bias. Future studies should evaluate the safety and efficacy of TOMAC in additional RLS populations, particularly those where a safer alternative to pharmaceuticals is especially needed, such as pediatrics and adolescents, pregnant women, patients with end-stage renal disease on hemodialysis, and individuals with mild or intermittent RLS. Real-world postmarket surveillance studies will be helpful to explore the longer-term safety and effectiveness of TOMAC. Another limitation is that patients on adjunctive medication in the TOMAC RCTs were required to remain on a stable dose, whereas most patients on dopaminergic medication would benefit from dose reduction to reduce risk of augmentation. Additional research is needed to determine if TOMAC could facilitate reduction in dopaminergic medication dose. Although heterogeneity was assessed and determined not to be significant, there were also design differences among the TOMAC RCTs, such as the inclusion of cross-over and non-cross-over trials, and study endpoints were evaluated at different timepoints (or not at all) across the relevant studies.

5. Conclusion

Currently, TOMAC is indicated for use for patients with moderate-severe RLS who are refractory to at least one medication. Our meta-analysis confirmed efficacy in this population and also demonstrated that TOMAC is similarly efficacious in non-medicated RLS patients (TOMAC monotherapy), patients with no previous exposure to RLS medication (medication naïve), and patients using TOMAC as adjunctive therapy to medication. Moreover, TOMAC efficacy was similar regardless of age, age of RLS onset, sex, baseline RLS severity, and stimulation frequency. Future research on TOMAC should include larger and longer-term real-world studies.

CRediT authorship contribution statement

Elias G. Karroum: Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Cornelius G. Bachmann:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Amy Bronstone:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration. **Leavitt Morrison:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This systematic review and meta-analysis study was sponsored and financially supported by Noctrix Health, Inc., and all authors received fair market value compensation for their contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2026.108810.

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