

Development of A Stepped-Care Pathway for Managing Willis-Ekbom disease/Restless Legs Syndrome during Pregnancy: A Best Evidence Synthesis

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APPENDIX 1 Search Strategy for Guideline Networks, Professional Society Websites, and Comprehensive English and Chinese Databases

APPENDIX 1.1 Search Strategy for Guideline Networks and Professional Society Websites

<p>JBI EBP Database</p>	<p>("Restless Legs Syndrome" or "Willis-Ekbom Disease" or "Ekbom syndrome" or "Wittmaack-Ekbom syndrome" or "RLS" or "WED" or "RLS/WED") and ("Pregnancy" or "Pregnancy Complications" or "Puerperium" or "Prenatal Care" or "Perinatal Period" or "pregnant" or "gestation " or "gestational" or "antenatal" or "prenatal" or "maternal " or "peripartum" or "postpartum" or "obstetric "). ab,kw,ti.</p>
<p>Other Guideline Networks and Professional Society Websites</p>	<p>("Restless Legs Syndrome" OR "Willis-Ekbom Disease") AND ("Pregnancy" OR "Pregnancy Complications" OR "Puerperium" OR "pregnant" OR "maternal")</p>

APPENDIX 1.2 Search Strategy for Comprehensive English and Chinese Databases

Databases	Search strategy
MEDLINE (via PubMed)	<p>#1 "Restless Legs Syndrome"[MeSH Terms] #2 "Restless Legs Syndrome"[Title/Abstract] #3 "Willis-Ekbom Disease" [Title/Abstract] #4 "RLS" [Title/Abstract] #5 "WED" [Title/Abstract] #6 "RLS/WED" [Title/Abstract] #7 "WED/RLS" [Title/Abstract] #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 "pregnancy"[MeSH Terms] #10 "pregnant"[Title/Abstract] #11 "maternal"[Title/Abstract] #12 "gestation"[Title/Abstract] #13 "gravidity"[Title/Abstract] #14 "conception"[Title/Abstract] #15 #9 OR #10 OR #11 OR #12 OR #13 OR #14 #16 "guideline"[Publication Type] #17 "guideline"[Title/Abstract] #18 "expert consensus"[Publication Type] #19 "expert consensus"[Title/Abstract] #20 "algorithms"[Publication Type] #21 "algorithms" [Title/Abstract] #22 "clinical decision-making"[Publication Type] #23 "clinical decision-making" [Title/Abstract] #24 "systematic review"[Publication Type] #25 "systematic review" [Title/Abstract] #26 "meta analysis"[Publication Type]</p>

	<p>#27 "meta analysis" [Title/Abstract] #28 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 #29 #8 AND #15 AND #28</p>
<p>Cochrane Central Register of Controlled Trials (CENTRAL)</p>	<p>#1 MeSH descriptor: [Restless Legs Syndrome] explode all trees #2 "Restless Legs Syndrome":ti,ab,kw #3 "Willis-Ekbom Disease" :ti,ab,kw #4 "RLS" :ti,ab,kw #5 "WED" :ti,ab,kw #6 "RLS/WED" :ti,ab,kw #7 "WED/RLS" :ti,ab,kw #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 MeSH descriptor: [pregnancy] explode all trees #10 "pregnant":ti,ab,kw #11 "maternal":ti,ab,kw #12 "gestation":ti,ab,kw #13 "gravity":ti,ab,kw #14 "conception":ti,ab,kw #15 #9 OR #10 OR #11 OR #12 OR #13 OR #14 #16 "guideline":pt #17 "guideline":ti,ab,kw #18 "expert consensus":pt #19 "expert consensus":ti,ab,kw #20 "algorithms":pt #21 "algorithms" :ti,ab,kw #22 "clinical decision-making":pt #23 "clinical decision-making" :ti,ab,kw #24 "systematic review":pt #25 "systematic review" :ti,ab,kw #26 "meta analysis":pt #27 "meta analysis" :ti,ab,kw #28 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 #29 #8 AND #15 AND #28</p>
<p>EMBASE (via Ovid)</p>	<p>#1 "Restless Legs Syndrome"/exp #2 "Restless Legs Syndrome":ti,ab,kw #3 "Willis-Ekbom Disease" :ti,ab,kw #4 "RLS" :ti,ab,kw #5 "WED" :ti,ab,kw #6 "RLS/WED" :ti,ab,kw #7 "WED/RLS" :ti,ab,kw #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 "pregnancy"/exp #10 "pregnant":ti,ab,kw #11 "maternal":ti,ab,kw #12 "gestation":ti,ab,kw</p>

	<p>#13 "gravity":ti,ab,kw #14 "conception":ti,ab,kw #15 #9 OR #10 OR #11 OR #12 OR #13 OR #14 #16 "guideline":pt #17 "guideline":ti,ab,kw #18 "expert consensus":pt #19 "expert consensus":ti,ab,kw #20 "algorithms":pt #21 "algorithms" :ti,ab,kw #22 "clinical decision-making":pt #23 "clinical decision-making" :ti,ab,kw #24 "systematic review":pt #25 "systematic review" :ti,ab,kw #26 "meta analysis":pt #27 "meta analysis" :ti,ab,kw #28 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 #29 #8 AND #15 AND #28</p>
China National Knowledge Infrastructure (CNKI)	<p>(篇关摘: 不宁腿综合征(模糊)) OR (篇关摘: 不安腿综合征(模糊)) OR (篇关摘: Willis-Ekbom 病(模糊)) AND (篇关摘: 妊娠(模糊)) OR (篇关摘: 怀孕(模糊)) OR (篇关摘: 孕妇(模糊)) OR (篇关摘: 孕期(模糊)) AND (主题: 指南(模糊)) OR (主题: 专家共识(模糊)) OR (主题: 诊疗流程(模糊)) OR (主题: 临床决策(模糊)) OR (主题: 系统评价(模糊)) OR (主题: meta 分析(模糊)) OR (主题: 证据总结(模糊))</p>
Wanfang database	<p>题名或关键词:(不宁腿综合征) or 题名或关键词:(不安腿综合征) or 题名或关键词:(Willis-Ekbom 病) and 题名或关键词:(妊娠) or 题名或关键词:(怀孕) or 题名或关键词:(孕妇) or 题名或关键词:(孕期) and 主题:(指南) or 主题:(专家共识) or 主题:(诊疗流程) or 主题:(临床决策) or 主题:(系统评价) or 主题:(meta 分析) or 主题:(证据总结)</p>
Chongqing VIP database (CQVIP)	<p>篇关摘=不宁腿综合征 OR 篇关摘=不安腿综合征 OR 篇关摘= Willis-Ekbom 病 AND 篇关摘=妊娠 OR 篇关摘=怀孕 OR 篇关摘=孕妇 OR 篇关摘=孕期 AND 主题=指南 OR 主题=专家共识 OR 主题=诊疗流程 OR 主题=临床决策 OR 主题=系统评价 OR 主题=meta 分析 OR 主题=证据总结</p>
China biomedical literature service system (SinoMed)	<p>"不宁腿综合征"[常用字段:智能] OR "不安腿综合征"[常用字段:智能] OR "Willis-Ekbom 病"[常用字段:智能] AND "妊娠"[常用字段:智能] OR "怀孕"[常用字段:智能] OR "孕妇"[常用字段:智能] OR "孕期"[常用字段:智能] AND "指南"[常用字段:智能] OR "专家共识"[常用字段:智能] OR "临床决策"[常用字段:智能] OR "诊疗流程"[常用字段:智能] OR "系统评价"[常用字段:智能] OR "meta 分析"[常用字段:智能] OR "证据总结"[常用字段:智能]</p>

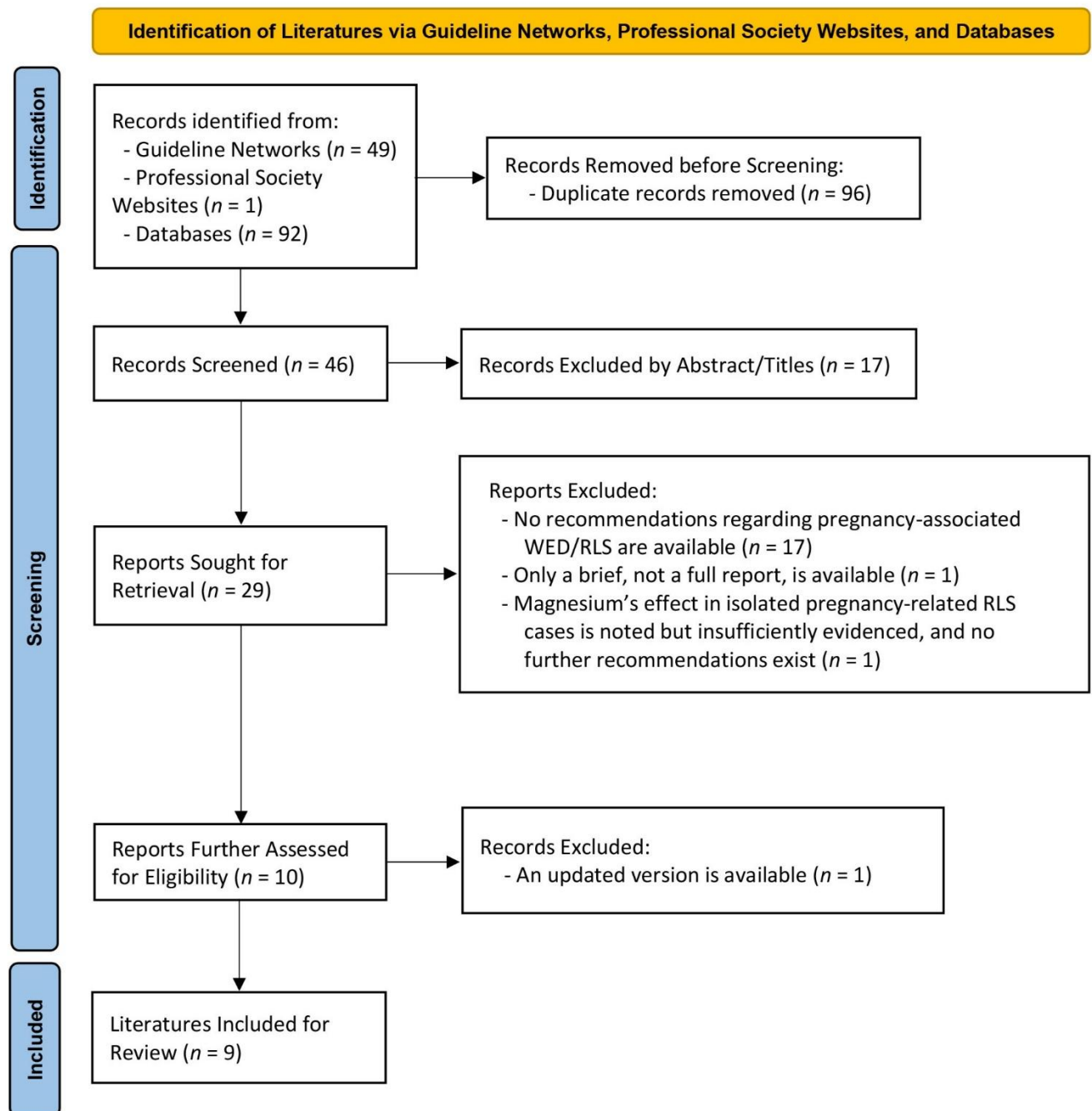
APPENDIX 1.3 The literature Search in This Study is Conducted in accordance with the PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Section 2.2 Evidence Retrieval
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	N/A
Study registries	3	List any study registries searched.	N/A
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	Section 2.2 Evidence Retrieval + Appendix 1 of the Supplementary Material
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	Section 2.2 Evidence Retrieval
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	Section 2.2 Evidence Retrieval
Other methods	7	Describe any additional information sources or search methods used.	Section 2.2 Evidence Retrieval
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Appendix 1 of the Supplementary Material
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Section 2.2 Evidence Retrieval

Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	2.3.1 Inclusion and Exclusion Criteria
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	N/A
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	N/A
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	Section 2.2 Evidence Retrieval
PEER REVIEW			
Peer review	14	Describe any search peer review process.	Dual-Person Retrieval and Screening (2.3.2 Literature Screening)
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Appendix 2
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	EndNote X20 (Section 2.3.2 Literature Screening)

Notes: PRISMA-S Checklist was adapted from *Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB; PRISMA-S Group. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. J Med Libr Assoc. 2021 Apr 1;109(2):174-200. doi: 10.5195/jmla.2021.962*. Creative Commons

APPENDIX 2 Flow Diagram of the Literature Selection



Notes: PRISMA Figure was adapted from Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 2021; 372: n71 doi:10.1136/bmj.n71. Creative Commons

APPENDIX 3 Characteristics of the Included Literatures

Author/Organization	Publication Year	Publication Language	Literature Resource	Type of Literature	Literature Theme
Chinese Physician Association Neurologist Branch Sleep Group <i>et al.</i> [13]	2021	Chinese	CQVIP	Guideline	Guidelines for the Diagnosis and Treatment of Restless Legs Syndrome in China (2021 Edition)
Garcia-Borreguero <i>et al.</i> [24]	2013	English	MEDLINE	Guideline	The long-Term Treatment of Restless Legs Syndrome/Willis-Ekbom Disease: Evidence-Based guidelines and clinical Consensus Best Practice Guidance: A Report from the International Restless Legs Syndrome Study Group
Gupta <i>et al.</i> [8]	2016	English	MEDLINE	Clinical Decision Aid	Restless Legs Syndrome and Pregnancy: Prevalence, Possible Pathophysiological Mechanisms and Treatment
Garbaza <i>et al.</i> [12]	2018	English	MEDLINE	Clinical Decision Aid	Management Strategies for Restless Legs Syndrome/Willis-Ekbom Disease During Pregnancy
Jahani <i>et al.</i> [7]	2020	English	MEDLINE	Evidence Summary	Management of Restless Legs Syndrome in Pregnancy and Lactation
Kaplan <i>et al.</i> [26]	2023	English	EMBASE	Clinical Decision Aid	A Neglected Area: Restless Leg Syndrome in Pregnancy and The Role of the Obstetric and Gynecology Nurse
Picchietti <i>et al.</i> [9]	2015	English	MEDLINE	Guideline	Consensus Clinical Practice Guidelines for the Diagnosis and Treatment of Restless Legs syndrome/Willis-Ekbom Disease During Pregnancy and Lactation
Silber <i>et al.</i> [27]	2021	English	MEDLINE	Algorithm	The Management of Restless Legs Syndrome: An Updated Algorithm
Zhuang <i>et al.</i> [25]	2023	Chinese	CNKI	Evidence Summary	Summary of Best Evidence for Management of Restless Legs Syndrome During Pregnancy

APPENDIX 4 Detailed Information for Excluded Literatures

References	Reasons for Exclusion
Allen RP, Picchietti DL, Auerbach M, Cho YW, Connor JR, Earley CJ, Garcia-Borreguero D, Kotagal S, Manconi M, Ondo W, Ulfberg J, Winkelman JW; International Restless Legs Syndrome Study Group (IRLSSG). Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. <i>Sleep Med.</i> 2018 Jan;41:27-44.	No recommendations regarding pregnancy-associated WED/RLS are available.
Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, Lamm CI, Tracy SL, Rosenberg RS; American Academy of Sleep Medicine. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. <i>Sleep.</i> 2012 Aug 1;35(8):1039-62.	No recommendations regarding pregnancy-associated WED/RLS are available.
Avni T, Reich S, Lev N, Gafer-Gvili A. Iron supplementation for restless legs syndrome - A systematic review and meta-analysis. <i>Eur J Intern Med.</i> 2019 May;63:34-41.	No recommendations regarding pregnancy-associated WED/RLS are available.
Chesson AL Jr, Wise M, Davila D, Johnson S, Littner M, Anderson WM, Hartse K, Rafecas J. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. <i>Sleep.</i> 1999 Nov 1;22(7):961-8.	No recommendations regarding pregnancy-associated WED/RLS are available.
Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keeffe S, Trenkwalder C, Högl B, Benes H, Jennum P, Partinen M, Fer D, Montagna P, Bassetti CL, Iranzo A, Sonka K, Williams AM; European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. <i>Eur J Neurol.</i> 2012 Nov;19(11):1385-96.	The statement "magnesium relieves symptoms in isolated cases of RLS secondary to pregnancy" is noted, but is based on insufficient evidence; no other recommendations regarding pregnancy-associated RLS are available.
Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, Hadjigeorgiou G, Inoue Y, Manconi M, Oertel W, Ondo W, Winkelmann J, Allen RP. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. <i>Sleep Med.</i> 2016 May;21:1-11.	No recommendations regarding pregnancy-associated WED/RLS are available.
Harrison EG, Keating JL, Morgan PE. Non-pharmacological interventions for restless legs syndrome: a systematic review of randomised controlled trials. <i>Disabil Rehabil.</i> 2019 Aug;41(17):2006-2014.	No recommendations regarding pregnancy-associated WED/RLS are available.

Huang C, Tang JF, Sun W, Wang LZ, Jin YS. Effectiveness of acupuncture in the management of restless leg syndrome: a systematic review and meta-analysis. <i>Ann Palliat Med</i> . 2021 Oct;10(10):10495-10505.	No recommendations regarding pregnancy-associated WED/RLS are available.
Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Li KK, Loubé DL, Morgenthaler T, Wise M; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. <i>Sleep</i> . 2004 May 1;27(3):557-9.	No recommendations regarding pregnancy-associated WED/RLS are available.
Naguy A, Alamiri B. Gestational Restless Leg Syndrome: In the Spotlight. <i>Prim Care Companion CNS Disord</i> . 2023 Jan 19;25(1):22br03235.	Only a brief, not a full report, is available.
Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, Rye DB; Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. <i>Mayo Clin Proc</i> . 2004 Jul;79(7):916-22.	An updated version is available.
Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, Costa J, Stiasny-Kolster K, Sampaio C. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. <i>Movement disorders: official journal of the Movement Disorder Society</i> . 2008 Dec 15;23(16):2267-302.	No recommendations regarding pregnancy-associated WED/RLS are available.
Trotti LM, Becker LA. Iron for the treatment of restless legs syndrome. <i>Cochrane Database Syst Rev</i> . 2019 Jan 4;1(1):CD007834.	No recommendations regarding pregnancy-associated WED/RLS are available.
Vignatelli L, Billiard M, Clarenbach P, Garcia-Borreguero D, Kaynak D, Liesiene V, Trenkwalder C, Montagna P; EFNS Task Force. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. <i>Eur J Neurol</i> . 2006 Oct;13(10):1049-65.	No recommendations regarding pregnancy-associated WED/RLS are available.
Winkelman JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, Zee PC, Gronseth GS, Gloss D, Zesiewicz T. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. <i>Neurology</i> . 2016 Dec 13;87(24):2585-2593.	No recommendations regarding pregnancy-associated WED/RLS are available.
Winkelmann J, Allen RP, Högl B, Inoue Y, Oertel W, Salminen AV, Winkelman JW, Trenkwalder C, Sampaio C. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017). <i>Movement Disorders</i> . 2018 Jul;33(7):1077-91.	No recommendations regarding pregnancy-associated WED/RLS are available.
Winkelman JW, Berkowski JA, DelRosso LM, Koo BB, Scharf MT, Sharon D, Zak RS, Kazmi U, Falck-Ytter Y, Shelgikar AV, Trotti LM, Walters AS. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline. <i>J Clin Sleep Med</i> . 2025 Jan 1;21(1):137-152.	No recommendations regarding pregnancy-associated WED/RLS are available.
Winkelman JW, Berkowski JA, DelRosso LM, Koo BB, Scharf MT, Sharon D, Zak RS, Kazmi U, Carandang G, Falck-Ytter Y, Shelgikar AV, Trotti LM, Walters AS. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. <i>J Clin Sleep Med</i> . 2025 Jan 1;21(1):153-199.	No recommendations regarding pregnancy-associated WED/RLS are available.

Xu XM, Liu Y, Jia SY, Dong MX, Cao D, Wei YD. Complementary and alternative therapies for restless legs syndrome: An evidence-based systematic review. <i>Sleep Med Rev.</i> 2018 Apr;38:158-167.	No recommendations regarding pregnancy-associated WED/RLS are available.
Zhou X, Du J, Liang Y, Dai C, Zhao L, Liu X, Tan C, Mo L, Chen L. The efficacy and safety of pharmacological treatments for restless legs syndrome: systemic review and network meta-analysis. <i>Frontiers in Neuroscience.</i> 2021 Oct 26;15:751643.	No recommendations regarding pregnancy-associated WED/RLS are available.

APPENDIX 5 Quality Appraisal Results for Clinical Practice Guidelines Using the AGREE II Instrument

Guidelines for Inclusion	Standardized scores for each area (%)						≥ 60% Number of Fields (number)	≥ 30% Number of Fields (number)	Recommended grade (level)
	Scope and Purpose	Participants	Rigor of Formulation	Clarity of Guidance	Guidelines for Applicability	Editorial Independence			
Chinese Physician Association Neurologist Branch Sleep Group <i>et al.</i> [13]	90.3	70.8	76.0	90.3	37.5	81.3	5	6	B
Garcia-Borreguero <i>et al.</i> [24]	75.0	40.3	82.8	84.7	65.6	100	5	6	B
Picchietti <i>et al.</i> [9]	91.7	61.1	87.5	88.9	60.4	100	6	6	A

APPENDIX 6 Quality Appraisal Results for Evidence Summaries Using the Revised CASE Worksheet

Domain	Item	Evaluation Results	
		Jahani <i>et al.</i> [7]	Zhuang <i>et al.</i> [25]
Summary topic	1. Is the summary specific in scope and application?	Yes	Yes
Summary methods	2. Is the authorship of the summary transparent?	Yes	Yes
	3. Are the reviewer(s)/editor(s) of the summary transparent?	Not completely	Not completely
	4. Are the search methods transparent and comprehensive?	Yes	Yes
	5. Is the evidence graded and is the system transparent and translatable	Yes	Yes
Summary content	6. Are the recommendations clear?	Yes	Yes
	7. Are the recommendations appropriately cited?	Yes	Not completely
	8. Are the recommendations current?	Yes	Yes
	9. Is the summary free of possible bias?	Yes	Not completely
Summary application	10. Can this summary be applied to your patient(s)?	Yes	Not completely
Quality of Evidence		High	Moderate

APPENDIX 7 Quality Appraisal Results for Algorithms and Clinical Decision Aids

Included Clinical Decision-Making/Algorithm	Study Type	Original Literature (CPG, Consensus, Systematic Review) on which the Clinical Decision/Algorithm is Based	Quality of the Original Literature	Quality of the Algorithm and Clinical Decision Aids
Gupta <i>et al.</i> [8]	Clinical Decision-Making	Guideline by Garcia-Borreguero <i>et al.</i> [24]	Level B	Level B
Garbaza <i>et al.</i> [12]	Clinical Decision-Making	Guideline by Picchietti <i>et al.</i> [9]	Level A	Level A
Kaplan <i>et al.</i> [26]	Clinical Decision-Making	Guideline by Picchietti <i>et al.</i> [9]	Level A	Level A
Silber <i>et al.</i> [27]	Algorithm	Guideline by Picchietti <i>et al.</i> [9]	Level A	Level A