Falsifiable Predictions / Experimental Tests

Hypothesis I - RLS Signals Originate in the Periphery / Sometimes Related to Edema Reabsorption				
Falsifiable Prediction	**Proposed Test**	**Predicted Result**	**Falsification Criterion**	**References**
Sxs[1] increase as leg edema volume decreases	Measure resolution of edema with a timed symptom log	Symptom onset coincides with volume loss	No temporal link between symptoms and volume change	Redolfi et al. 2009 [21]
Daytime graduated compression lowers Sxs that evening	Randomized daytime compression vs. sham stockings; evening IRLS	True compression lowers IRLS when compared to sham stockings	True compression is no different than sham stockings	Lettieri & Eliasson 2009 [22]
Evening pneumatic compression reduces Sxs	Double-blind vs. sham device with IRLS	IRLS decreased with active device compared to sham	Active device no better than sham	Lettieri & Eliasson 2009 [22]
Sxs vary with Interdialytic volume Δ's / ultrafiltration	Correlate volume removed with IRLS in HD patients	IRLS tracks with interdialytic volume Δ's / ultrafiltration	No relationship between Sxs and volume Δ's	Trenkwalder et al. 2016 [12], Dopierała et al. [23]
Sxs ↑ with chronic volume overload in HD patients	Correlate post-transplant volume Δ's with IRLS	IRLS tracks with huge volume Δ's post-transplant	No relationship between Sxs and volume Δ's	Winkelmann et al. 2002 [24]
Sxs peak with third-trimester edema, resolve at delivery	Track edema + Sxs during pregnancy and after delivery	Sxs parallel edema, resolve after delivery	No relationship between Sxs and edema	Manconi et al. 2004 [11]
Correcting SVI - induced edema reduces Sxs	Ablation of SVI, pre/post measure of edema / IRLS	Edema / IRLS drop after ablation	Edema / IRLS unchanged after confirmed ablation	Hayes, et al. 2008 [6]
Hypothesis II - RLS is an Interoceptive Homeostatic Emotion				
Falsifiable Prediction	**Proposed Test**	**Predicted Result**	**Falsification Criterion**	**References**
A small-fiber block abolishes RLS Sxs	Differential block of Aδ/C-fibers	Sxs abolished with confirmed block	Sxs persist despite confirmed block	Craig 2003 [25]
Sxs activate the dorsal posterior insula	Symptom-provoked fMRI	Graded posterior-insula activation with Sxs	No posterior-insula activation with Sxs	Ku et al. 2020 [24]
ACC tracks urge to move; insula tracks sensations	fMRI with separate urge and sensation ratings	Each region tracks with its dimension	Neither region tracks with its dimension	Astrakas et al. 2008 [27] Kim et al. 2020 [28]

[1] Sxs - RLS urges/sensations