

Understanding the future research needs in Postural Orthostatic Tachycardia Syndrome (POTS): Evidence mapping the POTS adult literature.

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ABSTRACT

POTS is under diagnosed with an estimated prevalence of 0.2%. North American and Australian researchers, as well as patient groups have called for more research into POTS. However, there has been no comprehensive appraisal of the current POTS evidence base.

Aim: To map the POTS evidence base.

Methods: Two reviewers systematically searched 12 databases until July 1st 2019 using the search term “Postural Tachycardia Syndrome” (n=7,280) and categorised the literature. Inclusion criteria included all adult published literature with no language restrictions. 779 papers are analysed and mapped.

Results: Seven themes were identified: symptomology and quality of life 16.8% (n=132), biomedical topics 16.5% (n=130), co-morbidities 10.3% (n=81), non-pharmacological management 9.8% (n=77), aetiologies 6.9% (n=53), pharmacological management 6.7% (n=53), and clinical management 6.6% (n=52). There 45 subthemes. Quality appraisal of the research studies (n=233) evaluated design, sample size, outcome measures, data analysis and research biases. 74.8% (n=175) were observational designs and 25.2% (n=59) were experimental designs (16 using a randomised controlled design, 11 of which had a sample size greater than 21). 47.4% (n=111) of studies only measured duration of effect for <1 day. 11.5% (n=27) of studies reported outcomes using an unvalidated subjective measurement tool.

Conclusion: The volume of adult POTS literature is small and the validity and reliability of the research lacks rigour. The evidence map methodology provides POTS researchers with a benchmark for research thus far. This paper adds an in-depth research appraisal to the broad calls for action, highlighting the pressing need for multicentre, good quality research in POTS, to support guidelines and consensus development in the future.

INTRODUCTION

It is 25 years since Postural Orthostatic Tachycardia Syndrome (POTS) was first recognised as a syndrome (1). To date, there remain large gaps in POTS research resulting in an incomplete understanding of POTS and hence limited validated interventions to support healthcare professionals in providing high quality care to POTS patients. This was starkly reflected in the 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope (2). The consensus statement has a very limited evidence base (2), with no level I treatment recommendations, two class IIA recommendations, five class IIB and three class III recommendations. There are still no licensed medications for POTS, an area identified both by clinicians (3, 4) and patient groups (5) as a high research priority. To improve POTS care and guidelines, there is a genuine need to both appraise and understand where POTS research stands today to help guide future research.

Schondorf and Low (1) first described POTS in 1993, identifying the hallmark postural related heart rate rise and associated orthostatic symptoms. The formal definition of POTS came in 1994 (6): “adults aged 18 or older with orthostatic heart rate increment > 30 bpm and symptoms of orthostatic intolerance”; symptoms are chronic (present > 6 months) with other potential causes excluded. Current diagnostic criteria in the Heart Rhythm 2015 consensus document defined POTS as a clinical syndrome characterized by:

- 1) Frequent symptoms on standing (consistent with a dysautonomia), including light-headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue.
- 2) A heart rate increase > 30 bpm from recumbent to a standing position held for more than 30 seconds (or >40 bpm in individuals 12 to 19 years of age), confirmed by either an active stand test for 10 minutes or tilt table testing.
- 3) The absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure), with the acknowledgment that a diagnosis of POTS and vasovagal syncope are not mutually exclusive (2).

The estimated U.S. prevalence of POTS is approximately 500,000 (7), with an average age at diagnosis of 17-35 years. POTS affects five times as many young women as men (8). Attempts to define prevalence accurately are hampered by existing research limitations resulting in its under diagnosis due to both clinician and patient awareness. Although the 2015 Heart Rhythm Society Consensus statement provided diagnostic criteria, they are somewhat limited in characterising the disorder fully. POTS can manifest in a variety of ways, and the imperfect diagnostic criteria further compound the problems of obtaining accurate estimates on prevalence, in part, due to misdiagnosis. Studies suggest between 11% (n= 303:33) (9) and 27% (n=59:16) (10) prevalence of undiagnosed POTS in patients labelled with chronic fatigue syndrome. One small study (n=35) found an association between POTS and hypermobile Ehlers-Danlos syndrome with an

estimated 50% overlap (11). It is not uncommon for healthcare professionals to misdiagnose anxiety as the cause of the tachycardia (12), and this was substantiated by the POTS UK Charity online survey (n=779) (5) which highlighted that 48% of respondents (n=374) received a misdiagnosis of psychological or psychiatric disorders.

POTS can be debilitating, having a significant impact on quality of life (13-15), comparable to that seen in people with long-term conditions such as chronic obstructive pulmonary disease and congestive heart failure (16). The abnormal postural heart rate rise means everyday activities are a struggle, making people with POTS exhausted, sleep deprived, depressed and in some cases suicidal (17-19). However, the symptom spectrum is broad, ranging from minimal to genuinely debilitating, highlighting the need for more nuanced research efforts to better understand POTS subtypes. Little has been reported on long-term outcomes; although POTS is a chronic condition, it is not known to have any excess mortality.

More recently, there has been some evidence of improved POTS diagnostic rates, attributed in part to an increased awareness and rise in POTS publications (20). There are broad calls for more collaborative funded research on POTS (21) and the need to improve awareness, treatments and research has also been echoed by patient groups (5, 13). To date, there is only one systematic review of effective therapies in POTS with an inclusion criteria of reported symptomatic response after more than four weeks of therapy (22). This systematic review included 25 case series (n >4) and 3 randomised controlled trials and concluded that POTS evidence is limited.

Research waste is a general problem with researchers either asking unsuitable questions in the context of the existing research, or ignoring published evidence (23). Evidence mapping is an increasingly used tool to support and guide researchers, helping to define future research agendas (23). The evidence map in our study was a systematic evaluation of the entire adult POTS evidence base and incorporated all published areas researched thus far (biomedical topics, aetiologies, clinical management, therapies, quality of life and co-morbidities), and included studies measuring effect under 4 weeks, irrespective of response to treatment.

Aim & Objectives

The aim of the POTS evidence map was to identify the literature, themes and research methods in the POTS adult literature to July 2019, thereby informing future research needs.

The objectives were:

- 1) To identify the literature and themes within published POTS literature.
- 2) To quality assess the research studies through mapping the research designs.

METHODS

Evidence mapping, initially reported in 2003 (24, 25) is a practical method to characterise the quality of research pertaining to a broad topic in medicine (24) and is defined as a systematic search of a broad field to identify gaps in knowledge and/or identify future research needs (23, 25, 26). The classic systematic review and meta-analysis generates specific, detailed information about a narrow question. In addition to capturing broad fields, evidence maps are specifically relevant for tackling areas lacking sufficient evidence and knowledge (25, 26) which is directly applicable to the current needs in POTS research. The broad calls to action in POTS research included no appraisal of the quality of research thus far to guide the future research needs. This evidence map contributes to the POTS research community's understanding of where we are to date and can be incorporated into research applications as supportive evidence, and by this means will improve the quality of future research.

Systematic search strategy

A protocol for a systematic literature search was approved by Coventry University Ethics and registered on PROSPERO (CRD42017057413). Searching of 12 electronic databases (PUBMED, MEDLINE, AMED, google scholar, CINHALL, COCHRANE review, ETHOS, PROQUEST (all databases), PSYCINFO, SAGE, SCOPUS, SPORTSDISC, and PEDRO) from inception until July 1st 2019 identified POTS literature from research studies, reviews, conference abstracts and debates on POTS. This strategy reduced the risk of publication bias (27), and sensitivity was increased by using a broad search term "postural tachycardia syndrome". Identification of additional studies was achieved through reference mining (28) and contact with the POTS UK charity, providing access to their reference library. There were no language restrictions placed. The appraisal identified similarities, differences, and the gaps across the literature. Starting broad and then narrowing down ensured a systematic approach. An experienced medical literature librarian assisted.

Screening

An electronic reference system allowed two reviewers (with expertise/training in POTS) to independently search, screen titles and abstracts. Inclusion criteria were adult literature (over the age of 18) with a reference to POTS made either in the title or abstract. For example, studies in chronic fatigue syndrome screening for undiagnosed POTS were included (9, 10). Published and unpublished literature was screened. Paediatric literature was excluded through reviewer hand searching rather than electronic database filtering, increasing search sensitivity. The internationally recognised PRISMA flow chart (29) was used to report the systematic search and selection strategy of the POTS literature for mapping uses (figure 1). 779 published papers, including POTS research studies, were mapped and narratively analysed.

Mapping the evidence

Review of the abstract and the full text (when required) synthesised the literature. The two reviewers agreed the themes pre- and post-review for mapping, used an iterative process, identified and independently verified papers (and included literature whether it was a review of a subtheme or a research study). Using content analysis, the literature (n=779) was quantitatively mapped into themes and subthemes. The published POTS research studies (sample sizes greater than five) (n=233) were mapped, analysed and presented separately using critical appraisal skills academy tools criteria (30).

RESULTS

Figure 2 is the mapped and synthesised POTS literature. The themes revealed were biomedical, aetiologies, medical co-morbidities, symptomology, and impact on quality of life, pharmacological and non-pharmacological management, POTS reviews from experts, and articles about POTS. The overarching themes were broken down into subthemes with a summation of the published observational and experimental research, and total collective sample sizes within each theme. Figure 3 is a map of the published POTS research designs. To appraise the quality of POTS research, studies were mapped to either observational or experimental methods, according to research design and total study sample size. Research was narratively analysed according to sample population, outcome measures, duration of measurement effect, analysis method, and bias.

Themes

The evidence map found seven themes across all the POTS literature. The highest volume of literature was about symptomology and quality of life 16.8% (n=132), followed closely by biomedical topics 16.5% (n=130). POTS treatments had a low volume of literature. This comprised of 17% of the total, of which 7% (n=53) evidenced pharmacological therapy and 10% (n=77) evidenced non-pharmacological management. Only 6.9% (n=54) of literature was on associated aetiologies and 10.3% (n=81) on overlapping conditions. There were 45 subthemes, summarised in figure 2, with the topic of cognitive dysfunction had the greatest publications (n=35) and the lowest volume of literature across four areas were: associations with Sjörger's Syndrome (n=2) and Lyme disease (n=3), midodrine (n=3) and compression treatment (n=4).

Research Study Designs

Figure 3 summarises the breakdown of the 233 published POTS research studies. The majority were observational studies 175 (74.8%) (i.e. they did not involve an intervention assessment on the part of the researchers), and there was a much smaller proportion of experimental studies (n= 59 (25.2%)) with assessment of a research intervention. Of the experimental studies 16 used a randomised control design, and of these, 11 reported a sample size greater than 21. Figure 4 demonstrates an increasing trend of POTS

related published research over the last 20 years. However, there was no published experimental research with a sample size greater than 100 and there were no qualitative studies (as of 1st July 2019).

Sample Population, size and characteristics.

The diagnosis of POTS met recognised criteria in all research studies (n=233) by either citing HRS guidelines or if the study was published prior to 2015, the authors reported POTS criteria meeting the subsequently developed HRS guidelines (2). The majority of the studies (n=216) included recognised POTS specialists in the authorship. In the observational and experimental studies, the total sample size was 9,359, of which there was a total sample size of 540 participants who completed randomised control studies. The sample populations represented the recognised POTS definition, however, there was under reporting of POTS aetiology, subtypes, or associated conditions, with reportage in only 47 (20.2%) of studies.

In general, data analysis was based on small sample sizes. There were only 45 (19.2%) observational studies using sample sizes > 100. Of these, 12 (5%) had sample sizes > 300 and seven of which were surveys, four retrospective studies and one, a non-interventional, prospective survey. In a significant body of the research to date the sample sizes were particularly small (<20 participants), n=104 (44.4%). Further analysis found sample sizes of 21- 40 in 40 studies (17.1%), sample sizes of 41-60 in 22 studies (9.4%), and sample sizes of 61-100 in 16 studies (7%).

Outcome Measures

There were a variety of objective measurements reported, with the highest number of data measurements taken from tilt table tests (32% n=75), followed by blood pressure and/or heart rate in 24 studies (10.2%) and active stand tests in 19 (8.1%). A variety of biomedical blood tests (n=123) and other objective measures; for example, polysomnography (n=5), VO₂ measurements (n=5), GI transit tests (n=6) and cerebral blood flow (n=3) were used. Objective measurements for effective treatment were taken at one point in time in half of the studies (n=113). Only a small number of studies measured treatment effect over longer durations; 24 studies (10.3%) took measurements within four weeks of treatment, and 23 studies took measurements between one to 12 months. Nine of the 23 studies were experimental and only two used a randomised control design with a sample size > 20.

Validity was significantly compromised by the heterogeneity of the ways in which subjective measurements have been taken and used. Data collection using only subjective measurements occurred in 35 studies (14.9%) comprised of 19 surveys (14 assessing symptomology and quality of life). A total of 71 studies (30.3%) took subjective measurements, 67 (25.6%) combined subjective data reporting with objective data. Data collection using more than one subjective measurement was frequently reported: 20 studies (8.5%) used between two to four subjective tools, and a further 13 studies collected subjective data

using more than 5 generic validated tools. A researcher's own unvalidated subjective tool was used with no corresponding objective data collection in 18 (7.7%) studies.

Reliability of POTS Research

Poor research design, small sample sizes and a variety of outcome measures limited data analysis. Descriptive statistics are used to report outcomes in almost a fifth of studies (18.3%, n=43). The P-value for statistical significance was calculated in 68.8% (n=161) of studies. Statistical significance was reached in 52.1% (n=122). However, 14 of these studies collected no objective measurements. Only 4 studies reported statistical significance and measured effective treatment for longer than one month. Confidence intervals were calculated in two studies. Of the seven systematic reviews (five published since 2018), six used narrative synthesis and analysis, with one study calculating meta-analysis solely based on heart rate (22). There was a lack of randomised controlled studies with large sample sizes that measured sufficient effect. This all leads to concerns regarding the reliability of POTS research, hampering both the clinical applicability and uptake of findings.

Research Teams

The trend over the past two years revealed increasing publication of collaborative research from a small number of specialist POTS centres in predominantly North America. 49.6% (n=116) of studies published originated from 6 North American researchers, and in total, North American researchers published 61% (n=144) of studies. European teams accounted for 20.5% (n=48). Overall, the adult POTS research is Western centric. Five studies (four published since 2018) represented collaborations across three countries, and 17 studies (eight studies published since 2018) represented collaboration between two countries. This signifies a more recent move towards multicentred research with global participation.

DISCUSSION

There have been international calls for research in POTS (5, 13, 21, 22, 31); a 2016 Australian publication (4), appealed for general improvements in POTS research designs, more registries and international research collaborations. The evidence map findings support these calls, and takes this further by identifying specific gaps in the literature and research design.

A POTS UK survey identified five patient research priorities (5). Figure 5 compares patient research priorities to: a) the Australian 2016 appeal (4), b) North American clinicians identification of the needs in POTS (3) and the evidence map findings. Interestingly, patients highest research priority was in lifestyle changes which are most effective to improve symptoms and patient's second priority was for research into the most effective medications. The clinicians' calls also identified effective treatments as a research priority, and the evidence map found a lack of research studies in pharmacological management (12.4%, n=29), with the least researched topic being non-pharmacological management (5.9%, n=14).

Both midodrine (an HRS IIb recommendation (2) based on three papers) and compression (not an HRS recommendation with four papers on compression) are treatments used in clinical practice; however, the systematic search found little literature on either. There was a substantial volume of literature on symptoms and quality of life, which included cognitive dysfunction in POTS, and these reflected clinical observations and patient accounts of the significant impact of POTS on quality of life (32). Unfortunately, correspondingly, literature on how clinicians can support and manage people with POTS was significantly lacking. Based on the lack of evidence in lifestyle changes and patients' priorities, further work is required into effective lifestyle changes.

Analysis of the themes (figure 2) identified areas where researchers could advance work with either a systematic review or additional research. Figure 2 provides a comparison for researchers investigating specific areas. For instance a published systematic review on the use of ivabradine for POTS has a combined study population of 132 based on 12 studies and one case study (33). This may seem low but comparing studies of efficacious treatments across the POTS mapped evidence base reveals a high study sample size in the use of ivabradine. Mapping POTS themes provides researchers with evidence supporting funding applications and a comparison for their research (see supplementary material).

In POTS there are different, poorly understood aetiologies making a faultless sample size difficult to attain. One broad call has been to improve the understanding of different POTS aetiologies (3), reflected in increasing research into autoimmunity and mast cell activation disorder (34-36). Publications in autoimmunity and POTS have almost doubled since 2018 from 11 papers to an additional 10 papers. However, there are other pathophysiologies not having received similar investigation. For instance, hypermobile Ehlers-Danlos syndrome (hEDS) represents a probable subtype of POTS, with a significant number of people reporting orthostatic intolerance (not necessarily POTS) (37). Our understanding and management of POTS in hEDS, compared to the autoimmune pathophysiology, is limited with four published papers since 2018. This has been compounded with insufficient reporting of sample population characteristics in the research, thereby hampering the understanding and management of the different pathophysiology's. Lack of reporting POTS aetiologies in research makes interpretation of study results and applicability to clinical practice challenging. Improving reporting will support better understanding of diagnostic criteria and classification of POTS subtypes, hopefully leading to targeted treatments. Future research needs to improve reporting of underlying aetiologies to develop a better understanding of the relationship with different comorbidities, and associated data on effective treatments' (5, 13, 21).

Control and measurement of variables in POTS can be difficult. Hydration, salt intake, menses, heat, physical conditioning, and diurnal variability all have an impact on heart rate and/or blood pressure (38). Taking objective measurements on a single day is an unreliable measure. Many studies reported solely subjective outcome measurements, and some studies used multiple subjective measurement tools. People with POTS report concentration difficulties, "brain fog" (39). To fill in multiple tools as part of a study in a condition impacting on concentration was clearly not a reliable research method or reasonable for

participants. Studies need to take account of these variables by taking measurements over a longer duration to establish cause and effect and should not report solely subjective outcome measures. There is a need for a validated subjective measurement tool or a validated generic subjective tool. It is not acceptable to use researchers' own tools, neither is it acceptable to use multiple generic tools for subjective measurements.

The Heart Rhythm Society guidelines on the management of POTS (2) were limited because of the research methods utilised. Clinical management is often based on clinical experience and reference to descriptive articles. Figure 2 shows 5.9% (n=46) of the entire POTS literature was an expert's narrative piece. As the awareness and therefore the diagnosis of POTS increases reflecting the current trend (figure 4), then possibilities exist to improve collaborative research on an international basis. Systematic searching and mapping of the evidence identified the problems with research design in POTS studies. The European Society of Cardiology (ESC) level I recommendations are derived from randomised control trials with adequate sample sizes, accurate reporting of sample characteristics, controls on variables, and clear outcomes. Research designs, including multicentre registries and randomised controlled trials, will further develop robust POTS research.

To support guideline development in the future, there is an imperative need to improve research methodology, and to improve current understanding. This can begin with collaboration on well-designed randomised studies and registries to determine if the current class IIA recommendations of a regular, structured progressive exercise program, and acute intravenous infusion of up to 2 litre of saline in short-term clinical decompensation, are effective treatments. Further investigation is required on the class IIB recommendations of a multidisciplinary approach to management, consumption of up to 2-3 litres of water, and 10-12g of sodium chloride daily. In clinical practice compression stockings are often recommended, however this recommendation was not in the guidance, requiring further study. The class IIB pharmacological recommendations (fludrocortisone, pyridostigmine, midodrine, propranolol and clonidine), are not licensed for POTS (40). Ivabradine has one of the best reported evidence bases in POTS requiring further investigation and recommendation (33). Further study of medication and non-pharmacological therapy is required given that the average POTS patient is a woman of child-bearing age and there is limited or no safety data in pregnancy for many recommended medications.

Study Limitations

The main limitation in this study is the use of evidence mapping which is a developing methodology. A systematic review narrows the focus to a precise question, whereas the evidence map provides data on a broad scale aiming to understand research needs. Research often uses poor research designs leading to lack of robustness in findings and conclusion validity; evidence mapping is a research tool increasingly being used (23). A PubMed search in October 2020 found 75 papers on evidence mapping with 37 (49%) of

publications published since January 2019. The POTS evidence map identified gaps and raised areas for research progression as outlined in the discussion, and is a contribution to the growing body of evidence.

Conclusion

Despite practical issues in conducting POTS research, there are improvements which can be made to research design to improve the validity and reliability, including larger, accurately recorded sample sizes, longer measurements of effect duration, and improved outcome measurements. There is now an urgent need to internationally expand the number of POTS researchers to other localities in addition to the ones which currently exist, including studying patients from non-tertiary care centres. POTS research needs to be international, multi-centred, and conducted by multiple research teams. The systematic search and evidence map provides an in-depth understanding of the issues and gaps in POTS research. The POTS evidence map is a benchmark for researchers, making evidence gathering easier for future research and supporting applications for research funding (23). The results provide data on the lack of high-quality POTS research informing our current understanding. It is incumbent on clinicians and researchers with an interest in POTS to address this in the future needs.

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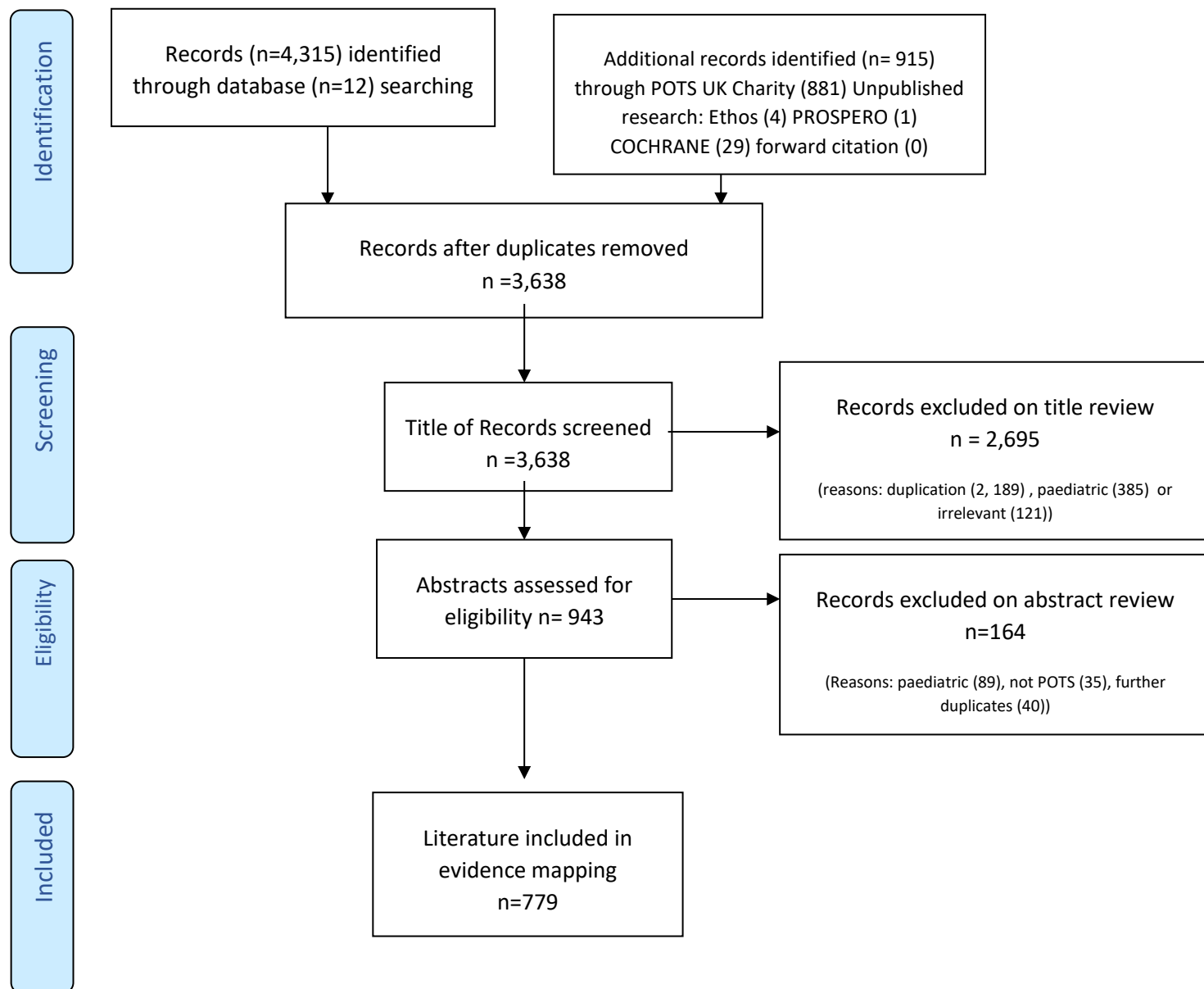
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PRISMA 2009 Flow Diagram (figure 1)



Theme & volume of literature published.	Subthemes expressed as a percentage of the total published work (n=779)	
Sub grouped into total published research studies and total participants.		
1) Symptomology & quality of life 16.8% (n=132)	Cognitive dysfunction 4.4% (n=35)	Sleep 1.7% (n=13)
Total research studies n=46	Impact on quality of life 4% (n=31)	Dermatological 0.9% (n=7)
Total participants n=14,889	Gastro-intestinal 3% (24)	Genito-urinary 0.8% (n=6)
Observational 100% Experimental 0	Migraine 2% (n=16)	
2) Biomedical literature 16.5% (n=130)	Sympathetic nervous system 3.8% (n=30)	Neuropathy (small fibre) 1.7% (n=13)
Total Research studies n= 66	Biochemistry (NET, ACE 1, NO) 3.3% (n=26)	Genetics 1.1% (n=9)
Total participants n=1,893	Autoimmune 2.7% (n=21)	Baroreflex / arterial stiffness 1.1% (n=9)
Observational n= 50 Experimental n= 16	Cerebral flow 2.3% (n=18)	Diurnal variability 0.5% (n=4)
3) Co-morbidities 10.3% (n=81)	Chronic fatigue syndrome 3.7% (n=29)	Fibromyalgia 0.8% (n=6)
Total Research studies n=17	Joint hypermobility / Ehler Danlos Syndrome 3.6% (n=28)	Mast cell activation disorder 0.8% (n=6)
Total participants n=701	Vasovagal syncope 0.9% (n=7)	Reactive hypoglycaemia 0.6% (n=5)
Observational n= 15 Experimental n=2		
4) Non-pharmacological management 9.8% (n=77)	Exercise 3.7% (n=29)	Compression 0.5% (n=4)
Total Research studies n=14	Fluids (water & IV saline 2.8% (n=22)	Isolated non-pharmacological interventions 0.8% (n=6)
Total participants n=784	Nutrition 1.1% (n=9)	Salt & sodium chloride 0.9% (n=7)
Observational n= 4 Experimental n=10		
5) Aetiologies 6.9% (n=54)	Human papillomavirus 4% (n=31)	Sjorgren's syndrome 0.2% (n=2)
Total Research studies n=33	Multiple Sclerosis 1.1% (n=9)	Lyme disease 0.4% (n=3)
Total participants n=1,590	Post-traumatic stress (incl. soldier's heart) 0.8% (n=6)	Lightening/ electrical 0.4% (n=3)
Observational n=30 Experimental n= 3		
6) Pharmacological management 6.7% (n=53)	Isolated pharmacotherapies 2% (n=16)	Midodrine 0.4% (n=3)
Total Research studies n=29	Beta-blockers 1.5% (n=12)	Pyridostigmine 0.5% (n=4)
Total participants n=560	Ivabradine 1.5% (n=12)	Octreotide 0.8% (n=6)
Observational n=7 Experimental n=22		
7) Clinical management 6.6% (n=52)	Pregnancy 2.2% (n=17)	Ablation 0.6% (n=5)
Total Research Studies n=29	Hyperadrenergic POTS 1.3% (n=10)	ECG significance to guide management 0.8% (n=6)
Total participants n= 984	Anaesthetic 1% (n=8)	Neuropathic POTS 0.8% (n=6)
Observational n=23 Experimental n=6		
Other literature 26.4% (n=210)	Article/ editorial / commentary/ book/ unpublished thesis 15.3% (n=119)	Isolated topics (no more than 1 publication in topic) 5.8% (n=45)
	Expert Overview 5.9% (n=46)	

Figure 2: The seven major themes in the POTS literature with volume expressed as a percentage of the total volume published on POTS (n=779). This is subcategorised to either observational and experimental studies and the total number of participants across each theme. Subthemes are quantified as a total percentage of the overall literature published on each topic. Volume of literature does not necessarily represent a definitive clinical association or treatment.

(Note: Two papers evaluate two different themes within one paper (therefore included twice in the map); two older papers evaluated three different interventions (41, 42))

<u>Observational studies</u>	Total	Sample size	<u>Experimental studies</u>	Total	Sample size
<u>Study Designs</u>	n=164	Total	<u>Study designs</u>	n=59	Total
		n=8,145			n=1,214
case control	79	2,108	intervention (no control)	11	234
cross-sectional	14	652	non-randomised (healthy control)	32	440
prospective cohort	10	1,119	Randomised	16	540
retrospective cohort	46	3,585			
systematic review	7	n/a			
Surveys with physician confirmed POTS diagnosis	8	681			
Surveys relying on patient reported POTS diagnosis (not included in totals)	10	12,505			

Figure 3: Breakdown of the research designs (n=233) used in POTS studies with total participant sample size.

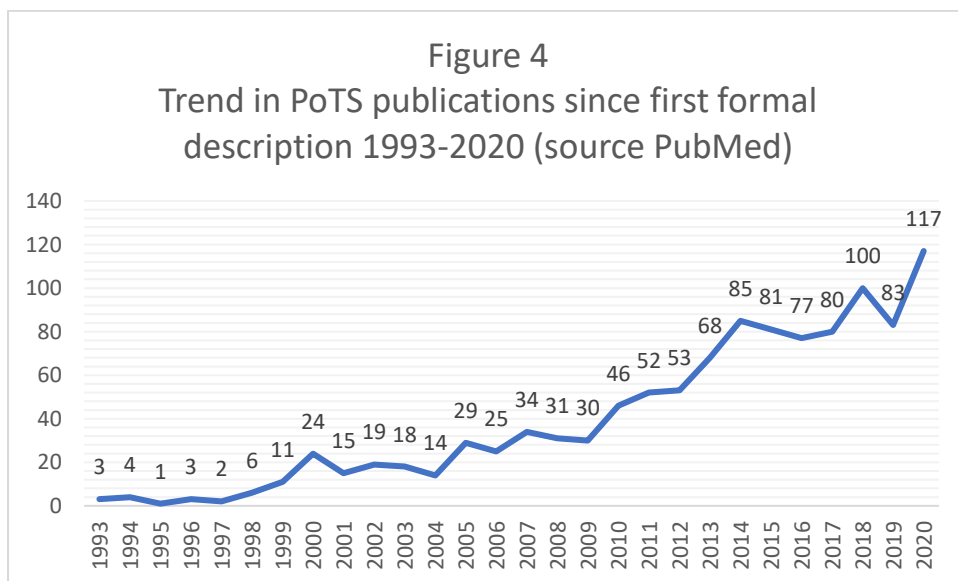


Figure 4: PubMed trend in POTS publications

Patient Research Priorities POTS UK Survey	Clinicians North America need identification	Clinicians Australian Call	Evidence Map findings of published research studies themes
1. What lifestyle changes are most effective to improve symptoms of PoTS? (28.9%)	1. Better understand pathophysiology's underlying POTS	1. Overcome diagnostic challenges	1. Biomedical literature Total studies n=66 (observational n=50 experimental n=16)
2. What is the most effective medication to treat POTS? (25.9%)	2. Better data on the number of PoTS patients and the impact of PoTS	2. Lack of Evidence- Based Management	2. Symptomology & quality of life Total studies n=46 (100% observational)
3. What causes POTS? (21.8%)	3. To improve physician awareness about PoTS to improve accurate diagnosis and access to care.	3. Need for Improved Collaborative Research	3 Aetiologies Total studies n=33 (observational n=30 experimental n=3)
4. What is the prognosis of PoTS? (16.6%)	4. Data on effective treatments for PoTS		5. Pharmacological management Total studies n=29 (observational n=7 experimental n=22)
5. How common is PoTS? (1.2%)	5. More research funding.		5. Clinical Management Total studies n=29 (observational n=23 experimental n=6)
other (5.6%)			6. Co-morbidities Total studies n=17 (observational n=15 experimental n=2)
			7. Non-pharmacological management Total studies n=14 (observational n=4 experimental n=10)

Figure 5: Patient research priorities from PoTS UK survey (5) compared to clinicians published identified research needs (3, 4) and the evidence map findings.