What is the role of TRPV1 receptor modulation in explaining the therapeutic relief experienced by Cannabinoid Hyperemesis Syndrome patients using hot water and capsaicin?

TRPV1 receptor modulation is proposed as a theoretical mechanism but lacks direct experimental evidence, with no studies measuring receptor activity in CHS patients to confirm it actually explains the therapeutic relief observed with hot water and capsaicin.

Abstract

Despite widespread clinical use of hot water and capsaicin for Cannabinoid Hyperemesis Syndrome, the evidence supporting TRPV1 receptor modulation as the mechanistic explanation for therapeutic relief remains predominantly theoretical rather than experimental. Only 3 of 10 studies provided substantive discussion of TRPV1 mechanisms , proposing that chronic cannabis exposure desensitizes TRPV1 receptors and that capsaicin or heat reactivate these receptors to deplete substance P signaling in the area postrema and nucleus tractus solitarius . However, this mechanistic framework relies on a single case report and in vitro cannabinoid studies rather than direct measurement of TRPV1 activity in CHS patients. The largest systematic review concluded that CHS pathophysiology remains unclear with limited evidence supporting any unifying mechanism, including TRPV1 . While hot water bathing demonstrates near-universal clinical effectiveness (91-92.3% of patients report relief), and capsaicin shows variable effectiveness depending on study design (100% response in small case series versus modest effects in larger retrospective studies), alternative explanations exist including CB1-mediated thermoregulation and natural symptom cycling. The evidence cannot definitively attribute therapeutic relief to TRPV1 modulation without controlled studies measuring receptor activity, substance P levels, or downstream signaling before and after interventions . TRPV1 activation remains a plausible but unproven hypothesis requiring prospective mechanistic studies rather than an established explanation for the observed clinical benefits.

Paper search

We performed a semantic search using the query ”What is the role of TRPV1 receptor modulation in explaining the therapeutic relief experienced by Cannabinoid Hyperemesis Syndrome patients using hot water and capsaicin?” across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We retrieved the 50 papers most relevant to the query.

Screening

We screened in sources based on their abstracts that met these criteria:

- **CHS Population**: Does this study involve patients diagnosed with Cannabinoid Hyperemesis Syndrome (CHS)?
- **Target Interventions**: Does this study investigate hot water therapy (hot showers, hot baths, topical heat application) or capsaicin (topical capsaicin cream, capsaicin-containing compounds) as therapeutic interventions for CHS?
- **Therapeutic Outcomes**: Does this study report therapeutic outcomes such as symptom relief, nausea reduction, vomiting cessation, or pain improvement?
- **Adult Population**: Does this study involve adult patients (≥18 years)?

- **Study Design**: Is this study a randomized controlled trial, cohort study, case-control study, case series, case report, systematic review, or meta-analysis?
- **CHS Specificity**: Does this study focus on CHS rather than solely on other hyperemesis conditions (e.g., hyperemesis gravidarum, cyclic vomiting syndrome) without CHS diagnosis?
- **Human Clinical Evidence**: Does this study include human clinical evidence rather than being solely an in vitro or animal study without human clinical correlation?
- **Original Research**: Is this study an original research article rather than a conference abstract, editorial, letter, or opinion piece without original data?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

  Extract the study type and evidence level including:

- Study design (case report, case series, systematic review, experimental study, etc.)
- Sample size and setting
- Quality of evidence (high, moderate, low based on study design and methodology)
- Any limitations acknowledged by authors

- **Patient Population**:

  Extract details about CHS patients studied including:

- Number of CHS patients
- Cannabis use characteristics (duration, frequency, type)
- Symptom presentation (nausea, vomiting, abdominal pain, cycling pattern)
- Demographics if relevant to mechanism (age, sex)
- Diagnostic criteria used for CHS

- **TRPV1 Mechanism Description**:

  Extract all details about TRPV1 receptor involvement including:

- Specific role of TRPV1 receptors described
- Location of TRPV1 receptors mentioned (area postrema, nucleus tractus solitarius, etc.)
- Molecular pathways involving TRPV1 (substance P signaling, etc.)
- How TRPV1 activation/modulation is proposed to affect CHS symptoms
- Any theoretical or experimental evidence supporting TRPV1 involvement

- **Hot Water Intervention**:

  Extract details about hot water treatment including:

- Description of hot water use (bathing, showering, temperature if specified)
- Frequency and duration of hot water use
- Timing of relief (immediate, delayed, duration of relief)
- Proposed mechanism connecting hot water to TRPV1 activation

- Clinical outcomes and effectiveness described
- Any adverse effects noted

- **Capsaicin Intervention**:

  Extract details about capsaicin treatment including:

- Capsaicin formulation (topical cream, concentration if given)
- Application method, location, frequency, and duration
- Dosing details if provided
- Timing and degree of symptom relief
- Specific outcomes measured (pain scores, vomiting frequency, etc.)
- Proposed mechanism linking capsaicin to TRPV1 modulation
- Any adverse effects or tolerability issues

- **Mechanistic Evidence**:

  Extract direct evidence linking TRPV1 to therapeutic relief including:

- Type of evidence (theoretical, experimental, observational)
- Specific biological processes described (receptor binding, desensitization, downstream signaling)
- Neuroanatomical pathways mentioned
- Biochemical or physiological measurements if any
- Strength of mechanistic evidence presented
- Alternative mechanisms considered or ruled out

- **Clinical Effectiveness**:

  Extract quantitative and qualitative evidence of therapeutic relief including:

- Specific outcome measures used
- Pre-post treatment comparisons with actual values
- Response rates or success rates
- Time to symptom relief
- Duration of relief
- Comparison with other treatments if available
- Failures or non-responders mentioned

- **Study Limitations**:

  Extract limitations that affect interpretation of TRPV1 mechanism including:

- Acknowledged study limitations
- Gaps in mechanistic understanding noted
- Confounding factors that could affect results
- Alternative explanations for observed effects
- Need for further research mentioned
- Generalizability concerns

Results

Characteristics of Included Studies

The included studies comprise a heterogeneous body of evidence examining TRPV1 receptor involvement in CHS therapeutic interventions. Study designs range from single case reports to systematic reviews, with most focusing on clinical outcomes rather than mechanistic investigation.

Study	Full Text Retrieved?	Study Type	Sample Size	Quality of Evidence	Key Limitations
Allison Lee et al., 2021	No	Retrospective review	57 patients	Moderate	Not mentioned
Douglas A. Simonetto et al., 2011	Yes	Case series	98 patients	Moderate	Single center, limited follow-up, retrospective bias
Laurel Dezieck et al., 2017	No	Case series	13 patients	Low	Not mentioned
C. Sorensen et al., 2016	Yes	Systematic review	183 articles, 211 patients	Low	Heterogeneity, lack of controlled studies, potential missing articles
Sean M. McConachie et al., 2019	No	Systematic review	18 patients in case reports/series	Low	Low methodological quality
A. Moon et al., 2017	Yes	Case report	1 patient	Low	Single case, incomplete follow-up
A. Pourmand et al., 2021	No	Systematic review and meta-analysis	106 patients across 7 studies	High	Need for RCTs
J. Richards et al., 2017	Yes	Systematic review	205 subjects across multiple studies	Low	Lack of high-quality studies, small patient numbers, publication bias
J. L. Stumpf et al., 2020	No	Review	Not mentioned	Cannot determine	Not mentioned
S. Nicolson et al., 2012	No	Case series and review	4 patients	Moderate	Diagnostic difficulties

The patient population across studies showed consistent characteristics: predominantly chronic cannabis users (95% used more than once weekly , with daily use documented), male predominance (72.9% , 67%), younger patients

(all under 50 years , median age at diagnosis 28 years), and cyclic nausea and vomiting with abdominal pain (100% experienced cyclic nausea/vomiting , 85.1% experienced abdominal pain). The hallmark symptom of compulsive hot water bathing was documented in 92.3% of patients , with 91% reporting relief with hot showers or baths .

TRPV1 Receptor Mechanism and Pathophysiology

The proposed role of TRPV1 receptors in CHS pathophysiology varies considerably across studies, with theoretical frameworks substantially outweighing experimental evidence. Three studies provided specific mechanistic descriptions of TRPV1 involvement, while the remaining literature either omitted TRPV1 discussion entirely or mentioned it peripherally.

Theoretical Framework of TRPV1 Involvement

The most comprehensive mechanistic model was presented by Moon et al., proposing that TRPV1 receptors are centrally involved in CHS pathogenesis . TRPV1 receptors are distributed throughout the gastrointestinal tract (on vagal sensory neurons, intrinsic enteric neurons, and gastric epithelial cells) and in high density at the area postrema, the chemoreceptor trigger zone . The proposed mechanism suggests that chronic cannabis exposure leads to TRPV1 desensitization through dephosphorylation , decreasing TRPV1 signaling and consequently altering gastric motility to produce emesis . This hypothesis is supported by in vitro studies demonstrating that exogenous cannabinoids lead to TRPV1 desensitization .

Two additional studies described TRPV1's role in therapeutic interventions. Dezieck et al. proposed that capsaicin binds TRPV1 with high specificity , impairing substance P signaling in the area postrema and nucleus tractus solitarius via overstimulation . Similarly, Richards et al. noted that TRPV1 receptors are found widely throughout the body in proximity to CB-1 receptors and that their activation regulates substance P release, a mediator of nausea and emesis . The activation occurs through low pH and high temperature , potentially explaining hot shower efficacy .

Evidence Gaps in TRPV1 Understanding

Seven of ten studies provided no information on TRPV1 receptor involvement , and among those that did, the evidence remained predominantly theoretical . The systematic review by Sorensen et al. noted only ”limited evidence” supporting TRPV1's interaction with the endocannabinoid system , while acknowledging that the pathophysiology of CHS remains fundamentally unclear with a dearth of research on underlying mechanisms . This represents a critical gap given that the research question specifically concerns TRPV1's mechanistic role.

Clinical Effectiveness of Hot Water Therapy

Hot water bathing emerged as a consistently effective intervention across multiple studies, though its connection to TRPV1 modulation remained speculative. Clinical outcomes demonstrated universal or near-universal effectiveness: 91% of 57 patients who tried hot water bathing reported symptom relief , and 92.3% of patients documented relief with hot baths or showers . Hot showers and baths were described as ”universally effective” in alleviating CHS symptoms .

The mechanistic explanation linking hot water to TRPV1 activation was explicitly proposed in only two studies. Moon et al. suggested that hot water bathing represents an attempt to normalize diminished TRPV1 activity through exposure to nociceptive heat, another TRPV1 agonist , with patients using up to 4 hours of hot water bathing daily . Richards et al. proposed that high temperature activates TRPV1 receptors, which may regulate substance P release . However, Simonetto et al. offered an alternative mechanism unrelated to TRPV1, suggesting that the relief involves

impairment of physiological thermoregulation due to cannabis use , potentially related to CB1 receptor effects on the hypothalamic-pituitary-adrenal axis .

No studies reported adverse effects from hot water bathing , though specific details on frequency, duration, temperature, or timing of relief were generally not provided .

Clinical Effectiveness of Capsaicin Therapy

Capsaicin interventions demonstrated variable effectiveness across studies, with response rates and outcome measures differing substantially based on study design and quality.

Case Reports and Case Series

Small case series reported uniformly positive outcomes. Dezieck et al. documented that all 13 patients experienced symptom relief after capsaicin administration following failed conventional treatments , representing a 100% response rate . Moon et al.'s single case study showed improvement in abdominal pain and nausea within a few hours of first application of 0.075% topical capsaicin , complete resolution of nausea after the second dose , and complete improvement of abdominal pain after the fourth dose , with sustained relief over three months . The application involved a 15 × 25 cm periumbilical area with reapplications every 4 hours .

The largest retrospective study by Lee et al. (n=57) found more modest results, with median pain scores decreasing from 8 to 5.5 , and 42% of patients requiring no further symptomatic therapy after capsaicin . Notably, capsaicin was administered relatively late in the treatment sequence (median 4 hours) , after antiemetics (median 1.6 hours) and opioids (median 1.8 hours) . No adverse drug events were reported .

Systematic Reviews and Meta-Analyses

The meta-analysis by Pourmand et al. examined 106 patients across 7 studies and found mean time to resolution of symptoms of 325 minutes and mean ED length of stay of 379 minutes following capsaicin administration . McConachie et al.'s systematic review identified capsaicin as effective in 18 patients across case reports and series , but notably, both retrospective cohort studies included in that review failed to find significant benefit on primary outcomes of ED length of stay . This discrepancy between study designs represents a critical finding, suggesting that case reports may overestimate effectiveness.

Sorensen et al.'s systematic review documented complete resolution of nausea and emesis in a case series of 5 patients using topical capsaicin cream applied to the abdomen , though evidence quality was limited . Richards et al.'s review reported successful treatment of seven patients with acute CHS using topical capsaicin , positioning capsaicin among the most frequently reported effective treatments after benzodiazepines and haloperidol .

Mechanistic Linking of Capsaicin to TRPV1

The proposed mechanism consistently involved TRPV1 activation across studies that discussed it. Capsaicin functions as a TRPV1 agonist , producing antiemetic effects through TRPV1 receptor activation . The anti-emetic effects are mediated by depletion of substance P from neural circuits traveling to the nucleus tractus solitarius , achieved through overstimulation of TRPV1 . This mechanism may help normalize diminished TRPV1 activity caused by chronic cannabis use .

The only reported adverse effect was skin burning noted by one patient , while other studies reported no adverse effects .

Synthesis: Reconciling Mechanistic Theory with Clinical Evidence

The literature presents a substantial disconnect between the proposed mechanistic role of TRPV1 and the actual evidence supporting this mechanism. This discrepancy manifests across multiple dimensions: quality of mechanistic evidence, consistency of clinical effectiveness, and the relationship between mechanism and outcomes.

Limited Mechanistic Evidence Despite Theoretical Plausibility

Only 3 of 10 studies provided substantive discussion of TRPV1 mechanisms , and among these, the evidence remained predominantly theoretical rather than experimental . The most detailed mechanistic proposal by Moon et al. rests on a single case report with acknowledged limitations of incomplete follow-up , and its supporting evidence consists of in vitro studies of cannabinoid-induced TRPV1 desensitization rather than direct demonstration in CHS patients. Dezieck et al. and Richards et al. proposed TRPV1-mediated substance P depletion , but neither provided experimental validation of this pathway in CHS.

The systematic review by Sorensen et al., despite evaluating 183 articles encompassing 211 patients , concluded that the pathophysiology of CHS remains unclear with limited evidence supporting any unifying mechanism, including TRPV1 involvement . This represents a critical limitation: if the largest systematic review finds insufficient evidence for TRPV1's role, the mechanistic explanation lacks the empirical foundation needed to conclusively explain therapeutic relief.

Study Design Hierarchy and Conflicting Effectiveness Evidence

The effectiveness of capsaicin shows a clear pattern based on study design quality. Case reports and small case series uniformly report positive results (100% response rate in one series of 13 patients , complete symptom resolution in another), while higher-quality retrospective studies show more modest effects (pain reduction from 8 to 5.5) or no significant benefit on primary outcomes . This pattern suggests potential publication bias favoring successful treatments and highlights methodological quality as a critical determinant of reported effectiveness.

The meta-analysis by Pourmand et al., rated as high-quality evidence , found acceptable time to symptom resolution (325 minutes) but explicitly called for further randomized controlled trials to adequately assess efficacy , indicating that current evidence remains insufficient despite including 106 patients. The systematic review by McConachie et al. similarly concluded that current data is of ”low methodological quality” , making capsaicin a reasonable adjunctive option primarily due to its favorable risk-benefit profile rather than robust efficacy evidence .

Alternative Mechanisms and the TRPV1 Attribution Problem

Multiple alternative explanations exist for the observed therapeutic relief, complicating attribution to TRPV1 specifically. Simonetto et al. proposed that hot water relief involves impaired thermoregulation through CB1 receptors in the hypothalamic-pituitary-adrenal axis , making no reference to TRPV1 . Richards et al. acknowledged multiple theories including dose-dependent hypothermic effects of THC on CB1 receptors and a ”cutaneous steal” syndrome , with the role of serotonin and histamine remaining unknown .

Moon et al. noted that previous models focusing solely on CB1 receptors are unsatisfying and fail to explain why only some patients are susceptible to CHS , but this gap in CB1-only models does not automatically validate TRPV1 as the primary mechanism—it simply indicates incomplete understanding. The complexity of capsaicin and TRPV1 receptor interactions remains not fully understood , and the proximity of TRPV1 receptors to CB-1 receptors suggests potential cross-talk rather than isolated TRPV1 effects.

Context-Dependent Effectiveness and Treatment Sequencing

The effectiveness of capsaicin appears context-dependent based on treatment sequencing and prior interventions. Lee et al. found that capsaicin was typically administered late in the treatment sequence (median 4 hours) , after antiemetics (nearly all 98% of patients received antiemetics) and opioids (47% received opioids) . The observed modest pain reduction may reflect either genuine capsaicin effects, natural symptom resolution over time, cumulative effects of multiple medications, or patient expectation effects following prolonged ED stays.

Dezieck et al.'s finding that capsaicin provided relief "after other treatments failed" could indicate either a genuine therapeutic effect or that patients reached the natural endpoint of their cyclical symptoms coincident with capsaicin administration. Without controlled studies comparing capsaicin timing and sequencing, these alternatives cannot be distinguished.

Gaps Requiring Resolution

The fundamental gaps in understanding TRPV1's role include: (1) absence of controlled studies measuring TRPV1 receptor activity before and after interventions ; (2) lack of studies comparing TRPV1 agonists with similar heat/irritant sensations that do not activate TRPV1; (3) insufficient mechanistic data on substance P levels, TRPV1 receptor density, or downstream signaling in CHS patients ; and (4) absence of studies explaining why hot water and capsaicin work through the same purported TRPV1 mechanism yet show different effectiveness patterns (hot water universally effective vs. capsaicin with mixed evidence).

The need for prospective studies to adequately assess capsaicin efficacy was explicitly noted , along with calls for basic science research to elucidate pathophysiology and large-scale randomized trials . Until such studies are conducted with direct measurement of TRPV1 activity, the mechanistic explanation remains a plausible but unproven hypothesis rather than an established mechanism explaining therapeutic relief.

References

A. Moon, S. Buckley, and N. Mark. "Successful Treatment of Cannabinoid Hyperemesis Syndrome with Topical Capsaicin." *ACG Case Reports Journal*, 2017.

A. Pourmand, Gabriel Esmailian, M. Mazer-Amirshahi, Owen Lee-Park, and Q. Tran. "Topical Capsaicin for the Treatment of Cannabinoid Hyperemesis Syndrome, a Systematic Review and Meta-Analysis." *American Journal of Emergency Medicine*, 2021.

Allison Lee, and Zlatan Coralic. "Use of Capsaicin Cream in Cannabinoid Hyperemesis Syndrome in Patients Presenting to the Emergency Department." *The Annals of Pharmacotherapy*, 2021.

C. Sorensen, K. Desanto, L. Borgelt, Kristina T. Phillips, and A. Monte. "Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review." *Journal of Medical Toxicology*, 2016.

Douglas A. Simonetto, Amy S. Oxentenko, Margot L. Herman, and Jason H. Szostek. "Cannabinoid Hyperemesis: A Case Series of 98 Patients." *Mayo Clinic Proceedings*, 2011.

J. L. Stumpf, and Lauren Williams. "Management of Cannabinoid Hyperemesis Syndrome: Focus on Capsaicin." *Journal of Pharmacy and Practice*, 2020.

J. Richards, Brent K. Gordon, Aaron R. Danielson, and Aimee K. Moulin. "Pharmacologic Treatment of Cannabinoid Hyperemesis Syndrome: A Systematic Review." *Pharmacotherapy*, 2017.

Laurel Dezieck, Z. Hafez, Albert Conicella, E. Blohm, M. J. O'Connor, E. Schwarz, and M. Mullins. "Resolution of Cannabis Hyperemesis Syndrome with Topical Capsaicin in the Emergency Department: A Case Series." *Clinical Toxicology*, 2017.

S. Nicolson, Lex Denysenko, J. Loretta Mulcare, Jose P. Vito, and B. Chabon. "Cannabinoid Hyperemesis Syndrome: A Case Series and Review of Previous Reports." *Psychosomatics*, 2012.

Sean M. McConachie, Ryan Caputo, S. Wilhelm, and P. Kale-Pradhan. "Efficacy of Capsaicin for the Treatment of Cannabinoid Hyperemesis Syndrome: A Systematic Review." *The Annals of Pharmacotherapy*, 2019.