# Navigating the waves of cluster headache: clinical aspects and GON modulation

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# GENERAL DISCUSSION: SUMMARY AND FUTURE PERSPECTIVES

## OUTLINE GENERAL DISCUSSION

The overarching aim of the studies in this thesis was to improve patient care by enhancing the ability of patients, physicians and researchers to "*navigate the waves of cluster headache*". This navigational challenge originates from the unique, oscillating enigmatic disease process in which storms (high disease activity with frequent attacks) alternate with calmer seas (remission (ECH) or attack reduction (CCH)). These *waves* create constant challenges: patients must find ways to cope and function despite unpredictable and painful attacks; physicians must adapt treatment strategies to shifting disease states; and researchers must capture and interpret findings against the backdrop of an unpredictable and ever-changing natural disease course.

This thesis approached *navigating the waves* in two stages. **Part I** focused on exploring the waves by deepening our understanding of the *clinical aspects of cluster headache*. Demographics of cluster headache were explored to uncover "*shapers of the waves*", factors that influence disease activity. These chapters covered substance use, risk-reward seeking behaviour, the natural disease course and hormonal differences in cluster headache. Additionally, the impact of the waves was explored, focusing on how quality of life was affected by cluster headache. **Part II** investigated *the breaking of the waves*, focusing on how *greater occipital nerve (GON) modulation affects cluster headache* by assessing its therapeutic potential and underlying mechanism.

In this final chapter, the main findings from both parts are brought together and placed into a broader context. Using the framework of the threshold hypothesis (Figure 1), it will be discussed how these findings influence the *waves of cluster headache* and the consequential implications for patients, physicians and researchers. Finally, we look ahead, outlining future directions and recommendations to improve navigation.

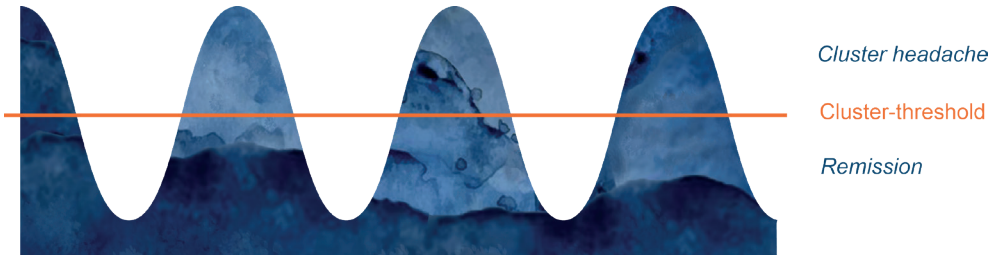


**Figure 1. Thematic visualisation of the threshold hypothesis.**

The fluctuating disease ativity of cluster headache, as suggested by the threshold hypothesis: Disease activity above threshold manifests as cluster headache and below as remission.

# PART I – EXPLORING THE WAVES
## CLINICAL ASPECTS OF CLUSTER HEADACHE

Having introduced the framework, **Part I** examines *the shapers of the waves* of cluster headache addressing how the disorder behaves over time (**Chapter 2**), substance use (**Chapters 3 and 4**), sex differences (**Chapter 5**) and quality of life (**Chapters 6 and 7**).

### The natural evolution of the waves

The combination of the complex pathophysiology of cluster headache and its fluctuating disease activity makes the (individual) natural course of cluster headache hard to predict. As a result, the frequently asked question—"*When will my cluster headache attacks finally stop?*"—cannot yet be answered. While the classification in subtypes (episodic or chronic cluster headache) provides a framework, individual disease courses vary.

To offer patients a meaningful answer, one must examine the three paths cluster headache can follow (Figure 2). The first path is *chronification* (1), episode continuation for at least a year resulting in chronic cluster headache. Chronic cluster headache can develop directly at first-onset or from episodic cluster headache.[1] Disease activity usually increases before chronification and smoking increases risk of chronification.[2] The most common trajectory falls between remission and chronification: *episode recurrence* (2). Episode recurrence is estimated at 0.29 to 2 per year.[3-12] For some patients, the attacks eventually recede entirely: *prolonged remission* (3). This can occur at any point, after a patients' first-ever cluster headache episode (~25%[13]) but also after decades. Studies on this topic require prolonged follow-up (often >5 years, ideally >15 years) which is less feasible prospectively.[13] Consequently, the few retrospective studies on this topic relied on small sample sizes collected by contacting patients until decades after their clinic visits to enable identification of prolonged remission.[13-18]

### When the waves recede — prolonged remission in cluster headache

The EPILOGUE study (**Chapter 2**) expanded insight into prolonged cluster headache remission and validated a scientific definition for prolonged remission to support its use in future studies. This study showed that prolonged remission often began when patients were around their mid-50s, typically after ~25 years of active disease. Not one unique pattern preceded prolonged remission: most reported an abrupt onset, while ~40% remitted after a gradual decreasing disease activity. Both age at remission onset and disease duration varied widely. Thus, the clinical observation that prolonged remission appears more common in older patients likely reflects cumula-

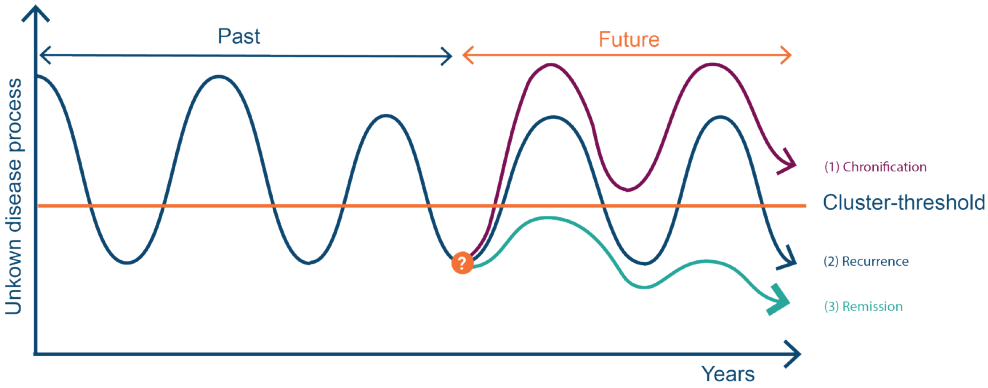


**Figure 2. Visualization of the three possible paths cluster headache can follow.**

(1) chronification (purple), episode continuation for at least a year resulting in chronic cluster headache; or
(2) episode recurrence (dark blue), the recurrence of episodes after a period of remission or
(3) prolonged remission (turquoise), in which the patient remains free of further episodes. Prolonged remission illustrated as a sustained period of subthreshold disease activity.

tive risk rather than a direct effect of ageing on remission. Unlike previous studies, **Chapter 2** identified factors associated with earlier prolonged remission, most notably the episodic subtype and smoking cessation, the latter supporting a causal link with disease activity (*revisited later in this discussion*).

### *Prolonged remission - Interpretation within the cluster threshold model*

Remission probability is higher in the episodic form, despite longer disease duration than in the chronic form. Attacks occur only when the fluctuating disease activity exceeds the cluster-threshold (Figure 2). In the episodic subtype, activity remains below this threshold more often, allowing remission periods; prolonged remission may represent an extended phase of subthreshold activity. Notably, most patients with a history of chronic cluster headache converted to the episodic subtype before prolonged remission, suggesting a gradual decline in disease activity. This decline may result from reduced hypothalamic activity via a complex interplay of factors. These include for instance altered connectivity to the suprachiasmatic nucleus, epigenetic changes, and fluctuations in vasoactive peptides and sex hormones.

## Substance use as potential drivers of the waves in cluster headache

Historically, persons with cluster headache have often been stereotyped as men with tattoos and daring personalities, with Dr. Graham describing them in the 70s as "*rugged, aggressive masculinity with bodies of sturdy, muscular mesomorphs*".[22, 23] Although such characterizations are now considered outdated and, of course, overly simplistic, certain aspects may still resonate with physicians. For instance, the high prevalence of smoking among cluster headache patients is hard to overlook. Whilst recognition of stereotypical traits may reflect confirmation bias, the etiology

of cluster headache remains elusive and warrants exploration of all leads, including patients' frequent reports of alternative treatments and illicit drug use.[24]

**Chapter 3** confirmed the previously largely anecdotal evidence that illicit drug use is more prevalent among people with cluster headache and showed that this is a cluster headache-specific phenomenon.[24-27] The question remains whether the increased prevalence is caused by an actual alleviatory effect, placebo response, conviction, or common pathophysiological background between cluster headache and addictive behaviours such as drug use. Below, we expand on the current hypotheses explaining the increased use of illicit drugs in the cluster headache population.

## Therapeutic efficacy of illicit drugs in cluster headache

For over three decades, reports on social media and a few peer-reviewed studies have suggested that psychedelics, such as psilocybin mushrooms (PSI) and lysergic acid diethylamide (LSD), may be therapeutic in cluster headache. Due to inefficacy of regular medicine and the reputation of these substances, many patients may be motivated to try illicit drugs, leading to an increased lifetime use regardless of perceived efficacy. Moreover, patients' self-perceived efficacy can be biased by their wish for a cure, resulting in a false conviction of benefit.

Psychedelic substances (e.g. PSI, LSD) have shown positive results, albeit primarily in small, uncontrolled studies and case series.[24, 29-31] Both PSI and LSD are thought to exert their effects through serotonin (5-HT) receptors, similar to sumatriptan, ergotamine and methysergide (Deseril®, a cluster headache medication that was withdrawn from the market to the dismay of patients). Sumatriptan acts predominantly on 5-HT1B and 5-HT1D receptors, leading to cranial vasoconstriction and inhibition of trigeminal neuropeptide release. Methysergide's therapeutic action was attributed to 5-HT1 agonism and 5-HT2B antagonism and the drug shared structural similarities to LSD. Likewise, LSD, shows high affinity for several serotonin receptor subtypes, including 5-HT1 and 5-HT2, suggesting a potentially shared serotonergic pathway in modulating cluster headache mechanisms.[32-34]

In **chapter 3**, the majority reported no effect of illicit drugs on attacks, with only a few positive responses following PSI and LSD use. Overall, larger randomized controlled trials are needed to clarify the efficacy and safety, as it remains unclear whether any potential alleviating effect truly explains increased illicit drug use.



### *Illicit drugs - Interpretation within the cluster threshold model*

Taken together, by acting on serotonin receptors, these substances could induce downstream mechanisms that temporarily elevate the cluster-threshold, resulting in a reduction (LSD/PSI) or abortion (sumatriptan) of cluster headache attacks. These

findings provide a mechanistic rationale for the potential clinical effects of serotonergic compounds.

## Does a 'Cluster Headache Personality' exist? – Risk-reward seeking behaviour in cluster headache

Another hypothesis for the increased illicit drug use is heightened risk-reward seeking behaviour in the cluster headache population. Anecdotal reports and several studies have suggested that people with cluster headache may share certain personality traits.[35-38] In the 1980s, the concept of a distinct "cluster headache personality" was debated, with clinicians attributing sensation-seeking, extroversion, and impulsivity as typical characterizations. This might explain the increased prevalence of illicit drug use in the cluster headache population. In contrast to patient's "*hyper-masculine*" physique, their personality was described by Dr. Graham as "*weak*", and as "*mice living in lions*".[23] Persons with cluster headache were reported to be more anxiety-prone, less socially successful, and more hostile, while also displaying a high analytic style marked by intense attention to stimuli, independent of other psychological factors.[35, 38] In contrast, other studies found no specific personality profile.[37] Therefore, it remains uncertain whether there are any personality traits associated with cluster headache, and if so, if they are primarily pre-existing characteristics, a result of living with cluster headache, or more likely a combination of both.[35]

Dysfunction in the hypocretinergic system, associated with the hypothalamus and regulation of functions, including sleep, addiction and nociceptive processing, may underlie both cluster headache and risk-reward seeking behaviour.[39-41] Interestingly, cluster headache was genetically correlated with measures of risk-reward seeking behaviour independently from its genetic link to smoking.[45] Against this background, **Chapter 4** examined risk-reward seeking behaviour in cluster headache by comparing results of surveys and behavioural task performances. We found that episodic cluster headache—especially in women—is associated with increased risk-reward seeking behaviour, supporting a possible biological vulnerability linked to both addictive behaviour and cluster headache. This tendency was less evident in chronic cluster headache, possibly reflecting a shift toward a more risk-averse lifestyle due to high disease burden.

## Smoking and Cluster headache

Both **Chapter 3 and 4** confirmed the high prevalence of smoking in cluster headache. This increased prevalence has long fueled debate about a possible causal role for tobacco exposure in cluster headache pathophysiology.

Smoking onset usually precedes cluster headache onset by 10–15 years.[46, 47] Additionally, childhood exposure to secondhand smoke appears to influence cluster headache susceptibility: the majority of individuals with cluster headache report at least one smoking parent.[46, 48] Tobacco exposure has also been associated with an earlier disease onset, suggesting that smoking, whether active or passive, may induce an irreversible susceptibility to cluster headache.[46, 48] Population trends in cluster headache prevalence appear to parallel historical smoking prevalence, including the trends in male-predominance of both.[12, 49] Although socioeconomic status is often associated with smoking behaviour, the cohort described in **Chapter 3** was relatively well educated, making socioeconomic status less likely as primary explanation.

Tobacco exposure in cluster headache patients is associated with a more severe phenotype, a later disease onset and a stronger rhythmicity.[12, 28, 50] Smoking however does not influence cluster headache immediately: most patients reported no change in smoking behaviour during episodes or remission periods.[50] This phenotypical distinction led to the hypothesis that smoking could influence cluster headache susceptibility via cadmium exposure, disrupting the hypothalamic–pituitary–gonadal (HPG) axis.[12] Cadmium can alter circadian regulation of hypothalamic clock genes (*Per1, Per2, Cry2*), potentially contributing to the strict periodicity of attacks.[12] Nicotine, another potent neuroendocrine HPG axis modulator, may exert similar influences. Thus, tobacco's toxic agents could contribute to cluster headache via direct hypothalamic toxicity, altered pain modulation, or interference with neuroendocrine and circadian systems. Another hypothesis might be that smoking might enhance hypoxia sensitivity.[51]

Genetic evidence, including a recent Mendelian randomization analysis, supports a causal role of smoking on cluster headache.[45] Additionally, genetic associations of smoking (namely, overexpression of *MERTK* and reduced expression of *CFTR*) mirror changes in the transcriptomic patterns observed in cluster headache.[45]

Although a common argument against a causal role of tobacco is that smoking cessation does not immediately cure cluster headache, **Chapter 2** showed that individuals who had quit smoking experienced earlier remission.[28, 49] Most patients, both in prior studies and **Chapter 2**, did not recognize quitting smoking as remission trigger.[49] Yet, the observed association with earlier remission suggested a true effect, potentially previously obscured by a delay in this beneficial effect. One explanation for the delay is epigenetic change: tobacco-induced DNA methylation patterns can persist for decades, and reversal after cessation is gradual, sometimes up to 30

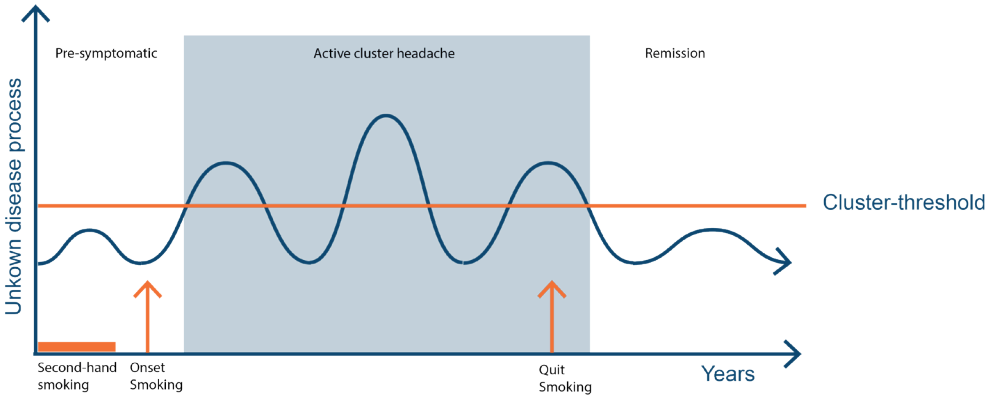


**Figure 3. Proposed influence of tobacco on cluster headache.**

Tobacco exposure (primary or secondarily via secondhand smoking) before cluster headache onset may gradually increase disease activity, eventually surpassing the threshold resulting in attacks. Cessation of smoking may allow slow biological recovery, reducing activity below the symptomatic threshold and permitting remission.

years, and may slowly reduce disease activity over time.[45] This slow trajectory would make the effect difficult to detect in short-term studies or by patient recall, despite its impact on the long-term course of cluster headache.

### *Smoking and disease activity - Interpretation within the cluster threshold model*

Initiation of smoking, or secondhand smoke exposure during childhood, before the onset of cluster headache may gradually drive disease processes towards increasing activity (Figure 3).[46] Over time, accumulation of pathological changes could push the system beyond a critical threshold, at which point cluster headache attacks manifest. Conversely, once smoking is discontinued, gradual biological recovery, potentially through reversal of DNA methylation, clearance of toxic compounds, or other restorative mechanisms, may slowly reduce disease activity. Over years to decades, this process might lower the cumulative burden below the cluster-threshold, allowing prolonged remission.

## Unraveling Sex Differences in Cluster Headache

Cluster headache has always been considered a male-dominated disease. But while male-to-female ratios ranged ~6:1 before the 60s, this has now declined to ~2:1 in Western countries.[3, 52] As a result, some suggest that sex hormones play a smaller role than previously thought. The increasing female predominance might be due to improved recognition of cluster headache in females and changes in environmental factors, such as smoking.[50, 53-55] This is supported by the absence of clear symptom changes during major hormonal events in women (menopause, pregnancy).[53]

As described previously, recent evidence linked smoking intensity causally to cluster

headache.[45] The higher proportion of male smokers may contribute to the male predominance in cluster headache.[50] The emergence of Asian datasets show different male-to-female ratios compared with Western populations. Interestingly, in Western countries, the rising female cluster headache prevalence parallels increased smoking rates among women, whereas smoking patterns remain largely unchanged in Asia, where the disorder remains predominantly male. That smoking might contribute to sex predominance is also supported by South Korean observations of less pronounced male-predominance among smokers than non-smokers.[54]

## Hypogonadism as explanation for male-predominance

In contrast to potential environmental drivers of male predominance, other evidence highlights the role of sex hormones: cluster headache onset is rare before puberty, and onset age overlaps with the male testosterone peak.[52, 56] This, in combination with anecdotes describing males with cluster headache as "hyper-masculinized," led to the hypothesis that androgens are involved in cluster headache pathophysiology.[22, 23]

**Chapter 5** evaluated hormone profiles and symptoms of androgen deficiency in cluster headache based on blood samples alongside surveys. Biochemical hypogonadism occurred predominantly chronic cluster headache and was often of a central origin, which is interesting given the hypothalamic–pituitary involvement in cluster headache.[57] Additionally, symptoms of androgen deficiency were more common in cluster headache, independent of biochemical hypogonadism.

Potential mechanisms for hypogonadism through hypothalamic-alterations, include elevated pituitary adenylate cyclase-activating peptide levels, which may impair gonadotropin-releasing hormone release via kisspeptin, reducing pituitary stimulation.[58, 59] Dopaminergic dysfunction may also play a role, with reported alterations in prolactin levels and cases where dopamine agonists normalized prolactin levels and resolved cluster headache.[60-62] Pituitary dysfunction may also result from structural lesions, with 77% of "symptomatic" cluster headache having lesions located in the pituitary region.[63]

Cadmium toxicity, caused by smoking, lowers testosterone, prolactin, growth hormone, and LH. This could suggest that reduced testosterone in cluster headache could be secondary to smoking rather than intrinsic to the disease.[12]

## Sex differences in the cluster headache phenotype

Beyond the male-to-female ratio in cluster headache, which has spurred hormonal research, there is increasing recognition of sex-related differences that extend be-

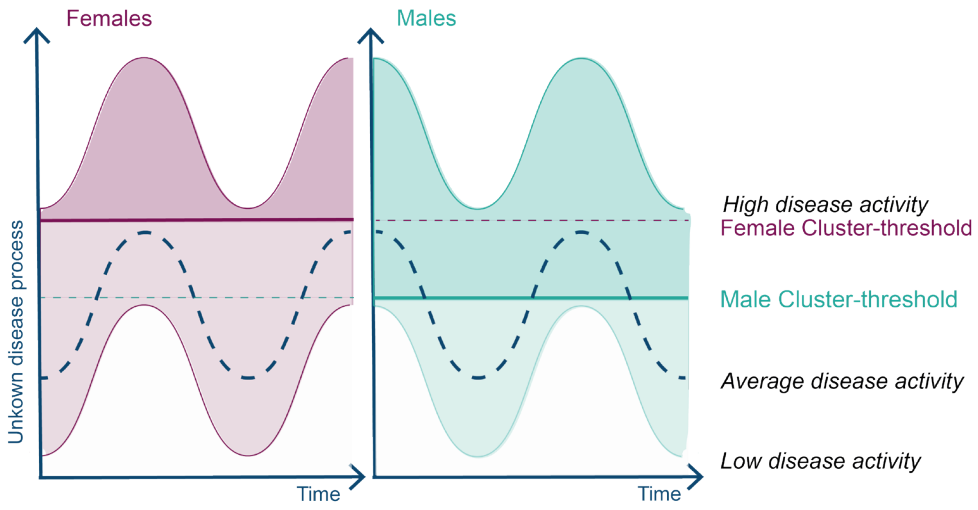


**Figure 4. Visualization of fluctuating cluster headache activity in females (purple) and males (turquoise).**

Disease activity varies over time and between individuals (range: low to high disease activity). Subthreshold periods correspond to remission (lighter color), while activity above threshold corresponds to attacks (darker color). Male predominance reflects a lower cluster threshold, whereas females generally have a higher threshold and lower prevalence; however, a small female subgroup exceeding the threshold experiences more severe disease.mitting remission.

yond hormonal profiles. These include distinct variations in the cluster headache phenotype between males and females. **Chapter 7** confirms that females have worse quality of life compared to males, due to a more severe clinical phenotype.[3] **Chapter 2** found no correlations with hormonal milestones (e.g. menarche, menopause), making a direct causal role for female hormonal fluctuations less likely.[64,53]

### *Sex-related differences: Interpretation within the cluster threshold model*

Overall, cluster headache shows a pronounced male predominance, which might reflect a lower cluster-threshold in males due to increased susceptibility caused by underlying pathophysiological factors (e.g. hypogonadism, smoking-related cadmium toxicity; Figure 4).

Females appear less frequently affected, possibly due to lower susceptibility, and thus a higher cluster-threshold for disease manifestation. However, when the cluster-threshold is exceeded, a female subgroup with particularly elevated disease activity emerges, resulting in a more persistent and severe clinical course (e.g., longer attacks, extended episodes, and higher proportion with the chronic subtype). Of course, it should be acknowledged that the increased threshold in females may be overestimated, because only those with severe disease activity might be recognized.

## The impact of the waves: quality of life in cluster headache

Remarkably little research has focussed on quality of life (QoL) in cluster headache, despite it being one of the most painful and disabling disorders.[65] During follow up, disease burden is mainly assessed by attack frequency, yet does not fully capture the impact. The absence of cluster-specific QoL questionnaire has long limited the use of patient-reported outcome measures (PROMs), as generic scales (e.g., EQ-5D, SF-36) capture the burden of cluster headache insufficiently, as they predominantly assess physical domains of QoL. This lack of appropriate tools has hindered research and recognition, leaving QoL poorly understood. Breaking this cycle is urgent, as evidenced by the results of **Chapter 4** that highlighting the high impact cluster headache has on QoL.[66] Encouragingly, updated clinical trial guidelines have increased recognition of the role of PROMs and recently, several cluster headache-specific QoL surveys have been developed, such as the Cluster Headache Quality-of-Life scale (CHQ) in 2016.[67, 68]

**Chapter 6** enabled implementation of cluster headache-specific QoL measurements in the Netherlands, by translating and validating the CHQ in Dutch. The resulting Dutch CHQ was subsequently implemented in ongoing research projects (*ONSFU cohort, NL75958.058.20; REGON cohort, NCT 05324748*). **Chapter 7** continued CHQ validation for measuring QoL changes in cluster headache.[69, 70] The results established the CHQ as a reliable tool to detect changes in QoL and provided guidance for score interpretation. It confirmed a weak correlation between attack frequency and perceived cluster headache burden.[71] QoL impairments in persons with cluster headache were mainly linked to pain, anxiety, depression, restrictions in daily socio-occupational activities and reduced vitality.[72] This aligns with a recent study where fear of attacks correlated stronger than attack frequency with the cluster headache burden, consistent with the Fear Avoidance Model (FAM) in which dysfunctional cognitive responses to pain amplify functional impairment.[73]

### *Quality of life: Interpretation within the Cluster Threshold model*

In conclusion, the present findings demonstrate that symptoms of cluster headache, such as attack frequency and attack duration, exert a measurable influence on QoL; however, the correlation between these variables is not one-to-one. Thus peaks in disease activity do not necessarily coincide with poor QoL, nor do dips invariably correspond with the highest QoL.

# PART II – BREAKING THE WAVES
## GON MODULATION IN CLUSTER HEADACHE

### Current evidence on efficacy of GON infiltration

**Part II** focusses on greater occipital nerve (GON) modulating therapies that "b*reak the waves*" of disease activity, providing patients (temporarily) relief from their cluster headache attacks. Earlier evidence of infiltration around the GON with corticosteroids was limited, and based on small, mostly unblinded studies with heterogeneous populations and varying treatment injectables and schedules.[74-82] With the addition of new randomized clinical trials (RCT), evidence for efficacy in the episodic subtype was strengthened, including the CHIANTI trial conducted in Leiden.[83, 84] Subsequently, GON infiltration has been increasingly applied in clinical practice and incorporated into the European guideline.[85] The mechanism by which GON infiltration prevents cluster headache attacks remains unknown. Hypotheses concerning possible mechanisms hereof are examined in **Chapter 8 and 9**.

### Neuroanatomical pathways targeted by GON infiltration

With increasing use of GON infiltration, a fascinating phenomenon has emerged: side-shifts after GON infiltration. Usually, attacks of cluster headache are side-locked, but in some patients, the side may shift between or – rarely - within cluster episodes. **Chapter 8** described previously side-locked cases in whom the side of attacks temporarily shifted immediately or shortly after unilateral GON infiltration with corticosteroids. This observation raises questions about the mechanisms underlying these temporary side-shifts: what enables side-shifts and how can they be induced by GON infiltration?

In order to address this, the neuroanatomical pathways underlying GON infiltration should first be considered. One could hypothesize that it modulates trigeminal transmission within the trigeminocervical complex (TCC). During attacks trigeminal circuits are overactivated, and the GON typically exerts an excitatory effect on these circuits. This effect might be reduced by "blocking" the GON with methylprednisolone.[86, 87] It may inhibit trigeminal circuits via a structural connection in the C2 spinal segments, where afferent nerve fibres of the GON (*blue* in Figure 5) and the trigeminal nerve (*orange*) converge in the TCC (*grey*). Clinically, this convergence is reflected in "referred pain", experienced as tenderness in the neck (GON region, blue), before pain radiates toward the peri-orbital region (V1 branch of the trigeminal nerve, orange).[86, 88-91] More centrally, the GON may exert its influence through the TCC to the hypothalamus (purple).[81, 92]

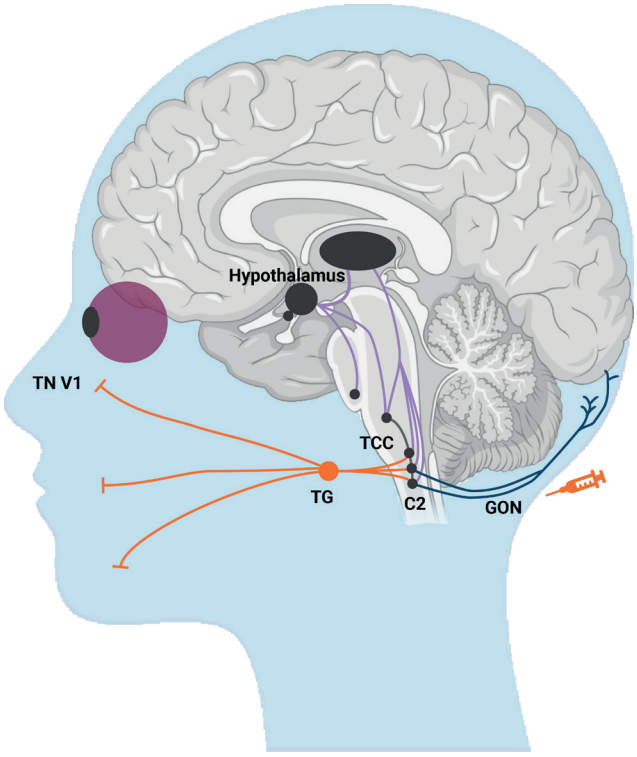


**Figure 5. Neuroanatomical pathways hypothesized to mediate the effects of GON infiltration in cluster headache.**

The syringe marks the infiltration site at the GON. Infiltration may inhibit trigeminal circuits via C2 spinal connections, where GON fibres (blue) and trigeminal fibres (orange) converge in the trigeminocervical complex (TCC, grey), and may also act through functional connectivity between the TCC and hypothalamus (purple). Abbreviations: C2 = spinal segments at C2 level; GON = greater occipital nerve; TCC = trigeminocervical complex; TG = trigeminal ganglion; TN V1 = ophthalmic branch of the trigeminal nerve.

## Neuroanatomical pathway of side-shifts induced by GON infiltration

Why cluster headache attacks are usually unilateral and side-locked is unknown. It has been postulated that both sides of the hypothalamus can act as an attack generator. During a cluster headache episode, one of the two hypothalami becomes more active and thereby suppresses the more dormant contralateral hypothalamus, resulting in clinical features only on the side ipsilateral to the active hypothalamus (Figure 6A).[93] When the dominant hypothalamus cannot suppress the other side sufficiently, a side-shift may occur. This hypothesis is supported by the observation that even outside a cluster episode the hypothalamic side ipsilateral to the attacks is hyperexcitable to external pain stimuli compared to the contralateral side.[94]

Unilateral infiltration of the GON with methylprednisolone reduces the normally present excitatory effect of the GON on the trigeminal system ipsilaterally. This results

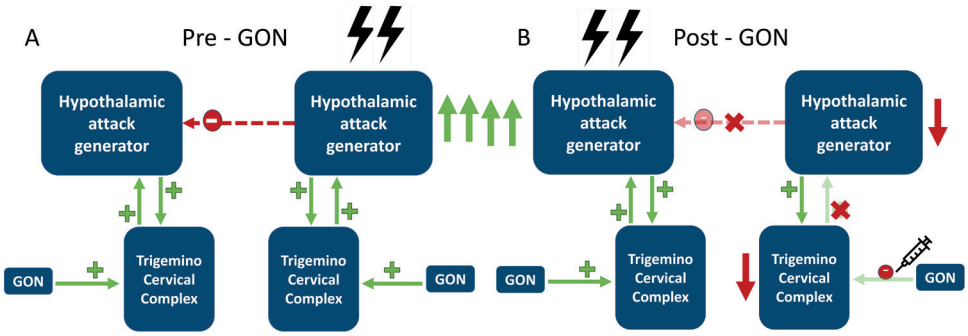


**Figure 6. Hypothesis of mechanism behind side-shift after GON infiltration.**

(A) Usual situation during cluster headache episodes: the hypothalamic attack generator ipsilateral to the clinical side of cluster headache attacks suppresses the contralateral hypothalamic attack generator.
(B): Unilateral injection of the GON with methylprednisolone causes attenuation of the excitatory effect of the ipsilateral GON and consequently a reduction of the activity of the ipsilateral trigeminal system, reducing the activity of the ipsilateral hypothalamic attack generator. In turn, this will result in (relative) overactivation of the "initially weaker" contralateral hypothalamic attack generator, causing a side-shift.

in reduced activity of the ipsilateral hypothalamic attack generator (Figure 6B). In turn, this will lead to (relative) overactivation of the "initially weaker" contralateral hypothalamic attack generator, causing a side-shift. Similarly, unilateral electrical neurostimulation of the GON can also cause a disturbance of this balance and consequently a side-shift.[95, 96] A spontaneous disturbance of the hypothalamic activity balance could explain spontaneous side-shifts.

## Trigeminal pathway modulation after GON infiltration

**Chapter 9** tested the hypothesis that GON infiltration influences trigeminal transmission in cluster headache. This was examined with the R2 component of the blink reflex, where prolonged latency—indicating delayed transmission through the TCC–GON conjunction—was expected to be associated with clinical response. **Chapter 9** confirmed efficacy of GON infiltration, but nor R2 latencies nor other neurophysiological measures correlated with clinical outcomes. Therefore, despite rigorous analysis, no evidence was found that the clinical response of GON infiltration is caused by reduced - or modulated - transmission of the trigeminal nerve or the TCC.

### *GON infiltration - Interpretation within the cluster threshold model*

Patients often report that GON infiltration may "block" attacks by elevating the cluster-threshold, preventing progression from pre-attack symptoms into a full-blown attack. Although the precise mechanism remains elusive, the occurrence of side-shifts after infiltration suggests modulation of hypothalamic activity rather than acting primarily through trigeminal transmission; an interpretation further supported by the absence of measurable changes in trigeminal transmission.

## NAVIGATING THE WAVES
## FUTURE PERSPECTIVES IN CLUSTER HEADACHE

In the text above we summarized the main results of this thesis and, using the threshold model, placed them in a broader context to show how they affected the waves of cluster headache. In this final part, the focus shifts to clinical recommendations and priorities for future research that aim to steer patients, physicians, and researchers towards better patient care, by improving their ability to *navigate the waves of cluster headache*.

Navigation rests on two complementary approaches: *exploring the waves*, which entails advancing knowledge of **pathophysiology** and **prognosis**, and ***b**reaking the waves*, which focuses on **prevention** and **psychological adaptation**. Looking ahead, progress in both approaches will be essential: more accurate charting and prediction of disease activity, alongside more effective strategies to reduce attack frequency and strengthen patients' coping capacity.

Therefore, we outline recommendations to enhance *navigation of the waves* through targeted innovations across four interrelated domains :

1. **Pathophysiology**: deepen the understanding of the disease process
2. **Prognosis**: improve prediction of peaks and remission periods
3. **Prevention**: reduce disease activity or raise the cluster threshold to prevent attacks
4. **Psychological Adaption**: empower patients by providing tools to better cope with the impact of cluster headache

# PART I - EXPLORING THE WAVES
## PROGNOSIS AND PATHOPHYSIOLOGY

Building on the findings of **Part I**, this section provides future directions for continuing *exploring the waves of cluster headache*. Firstly, potential avenues to advance understanding of the **pathophysiology** are described. Second, ways to improve prediction of **prognosis** are discussed that could help patients, physicians, and researchers anticipate fluctuations and navigate the waves more confidently. Insights from both approaches can reinforce each other, ultimately enhancing patient care.

### 1. Pathophysiology

To develop curative therapies, a deeper understanding of the underlying disease mechanism is essential. The disease process of cluster headache is driven by multiple factors that accumulate and ultimately escalade in cluster headache attacks once the threshold is exceeded. Several items have been suggested as potential mediators of this process, the so called *shapers of the waves*. These include sleep/circadian rhythms, tobacco exposure, sex hormones and the hypothalamus. However, their potential roles are inferred from correlation rather than causal evidence.
Unfortunately, causal research in cluster headache remains challenging. While genetic studies confirm a heritable, polygenic component, no monogenetic cause has been identified, unlike migraine where pathogenic variants in CACNA1A, ATP1A2, and SCN1A cause familial hemiplegic migraine.[98, 99] The absence of a single causal mutation prevents the use of knockout animal models, hindering mechanistic insights and curative treatment development, challenging researchers to find alternative models.

#### *Proxy models of cluster headache*

Although no animal model fully simulates cluster headache, targeting implicated pathways can serve as useful *proxies*. Mouse models targeting trigeminal nociception or hypothalamic signaling, for example, provide alternatives for causal inference in the absence of a genetic knockout model. The only described preclinical cluster headache model stimulated trigeminal-vascular pathways to induce autonomic symptoms, illustrating how separate components of the pathophysiology can be studied experimentaly.[100] Migraine models also remains informative due to shared downstream pathways, though translation is limited, as shown by the disappointing efficacy of CGRP-targeted therapies in cluster headache. Beyond animal models, post-mortem studies could yield unique insights into neuronal or glial alterations, neuropeptide expression, or heavy metal accumulation.

#### *In-patient models: wearables and home-monitoring devices*

Demographic studies have identified potential shapers of the waves, such as smoking, but causal research into these factors often stagnates. The tobacco–cadmi-

um hypothesis, for example, remains untested despite decades of discussion (e.g. testing comparing urinary cadmium levels or depositions in the brain between tobacco-exposed and non-exposed patients).[12] Progress is limited by complexity, cost and burden of prospective study designs. If studies are conducted, they are often underpowered with conflicting and difficult-to-interpret results, further demotivating researchers. Greater progress may be achieved by studying these factors in an integrated, multifactorial context —studying multiple simultaneously— instead of the current isolated approach, as most *shapers* are likely interrelated contributors rather than isolated drivers. Emerging technologies, including wearable devices and home-based monitoring tools, can be seen as '*in-patient*' models of cluster headache, allowing simultaneous in vivo collection of data on multiple *shapers*. This could facilitate distinction between primary drivers and downstream consequences. The ongoing CIESTA study (*NL84386.058.23*) exemplifies this approach by combining simultaneous portable sleep recording, core body temperature and micro dialysis to explore the interplay between sleep, circadian rhythms, and cluster headache attacks.

### *Multi-omics models*

A promising avenue lies in integrating multimodal "omics" datasets into *multi-omics* models that capture interconnected layers of human biology (genomics, epigenomics, transcriptomics, proteomics, metabolomics). Currently most omics have been studied in isolation: genomic approaches have investigated the causality of smoking, while proteomic analyses have identified potential causally involved proteins and examined domains such as sex hormones, inflammatory markers or vasoactive neuropeptides.[45,101-104] Since individual examination is insufficient to fully understand the pathophysiology of cluster headache, integrating multi-omics data is necessary. Multi-omics data, analyzed using advanced statistical and computational methods, can increase statistical power though pooled datasets and disentangle complex interactions between disease modulators. Thus multi-omics data could reveal hidden biological pathways that remain hidden when studied separately.

### *Innovation and integrating: future modeling?*

In summary, numerous opportunities remain for future pathophysiological research in cluster headache, whether through "*proxy*", "*in-patient*", or "*multi-omics*" models. Beyond the model's specific challenges, several obstacles apply across all approaches including the need for standardized sample collection with comprehensive metadata, and international collaboration to overcome small sample sizes. Linking insights across models can achieve understanding of underlying pathways and inform the development of a comprehensive 'experimental' model of cluster headache, whether computational, in vitro, or both. For example, patient derived induced pluripotent stem cells (iPSCs) brain organoids might be a promising in vitro model for mechanistic cluster headache research and help accelerate translational research

toward uncovering disease mechanisms and novel therapies.[105]

## 2. Prognosis: Towards Prognostic Models in Cluster Headache

One of the major determinants of poor quality of life in cluster headache is unpredictability of attacks. Most patients express a strong desire to know their prognosis. Reliable prognostic tools would be valuable not only for patients, but also for physicians, who could adapt management strategies in advance, and for researchers, who could better distinguish treatment effects from the natural course of the disease.

### *1. Prospective monitoring and digital tools*

A first step towards improving prognostic knowledge is to study the disease course prospectively, as retrospective data are limited by recall bias. Prospective data collection using weekly electronic diaries would improve accuracy, particularly when combined with regularly updated information on medication use, smoking status, and 3-monthly quality of life surveys. Such data could clarify temporal relationships—for instance, whether quitting smoking alleviates cluster headache—and generate real-world evidence on the efficacy of existing treatments, many of which lack randomized controlled trial data. In addition, new digital tools and wearables offer opportunities to identify prodromal changes, enabling earlier intervention (e.g. timely abortive treatment), which may shorten attack duration. Similarly, prediction of episode onset could enable earlier initiation of preventive therapy and reduce the anxiety many episodic patients experience when anticipating an impending cluster period.

### *2. Integration of multimodal datasets to improve predictive and stratified models*

Beyond prospective monitoring, pooling datasets across studies to create larger more comprehensive cohorts could improve predictive models. Predictive markers that appear weak in isolation may become meaningful in combination (e.g., hormonal profile together with tobacco exposure predicting a severe disease trajectory). Moreover, integrated datasets may reveal clinically meaningful subgroups, or endophenotypes, defined by a combination of biochemical markers, clinical characteristics, and lifestyle factors that differ in disease course and treatment response. Stratification in this way could guide more personalized treatment, reduce exposure to ineffective therapies, and improve overall outcomes.

### *Toward prognostic models to predict disease course and treatment response*

In summary, integrated multimodal prospective models could improve (individual) prognosis of disease trajectories (recurrent episodes, chronification, remission) or probability of treatment response. In clinical practice, they could give patients more control, physicians guidance in decision-making and researchers improved trial efficiency through improved patient stratification.

## PART II - BREAKING THE WAVES
FOCUS ON PREVENTION AND PSYCHOLOGICAL ADAPTION

Building on the findings of **Part II**, this section focuses on recommendations to improve *breaking the waves* of cluster headache through **prevention** and **psychological adaptation**. Enhancing preventive interventions can reduce attack frequency and duration, while interventions that improve psychological adaption empower patients to cope better with the impact of the remaining attacks.

### 3. Prevention: Recommendations for Future Research and Preventive Strategies in Cluster Headache

In the absence of a curative treatment, management of cluster headache focuses on attack prevention. In the framework of the threshold-hypothesis, interventions may prevent attacks by raising the cluster threshold (e.g., patients reporting post-intervention: "*I feel attacks starting, but they do not break through*"), it may dampen disease activity, or both (Figure 8). In the search for better treatment , existing therapies can be further optimized and potential *shapers of the waves* could be investigated as novel therapeutic targets.

### Study design and outcomes measures

Research into preventive interventions for cluster headache using RCTs remains particularly challenging. To support researchers, the International Headache Society (IHS) published updated guidelines in 2022, providing recommendations on study design to better account for the naturally fluctuating disease course.[67] A key aspect of this challenge is a relatively high placebo response (~30%) in cluster headache compared to the expected treatment response (responder commonly defined as

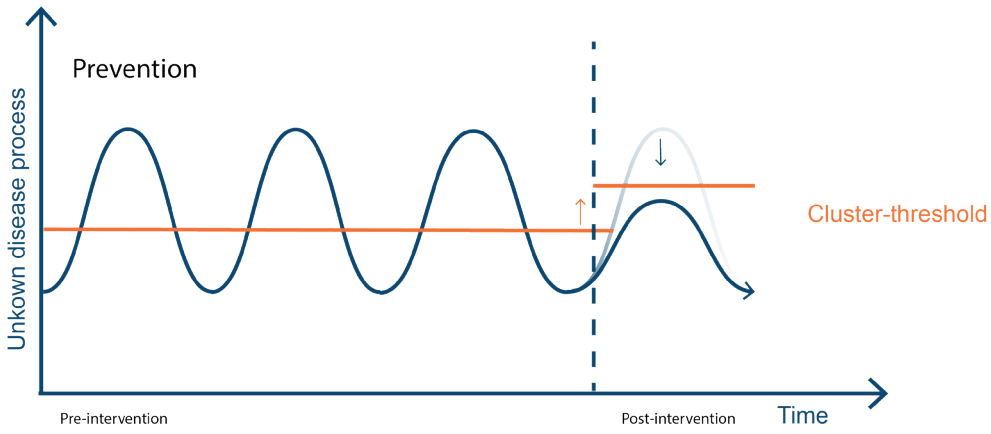


**Figure 8. Prevention may act by raising the cluster threshold and/or it may dampen disease activity.**

~30-50% reduction).[106-108] This may reflect the cyclical nature of the disorder, as patients often enroll during peak disease activity followed by natural regression, combined with strong treatment expectations due to the disease severity.[109, 110]

A further recommendation, is to include cluster headache–specific QoL instruments in addition to headache diaries.[67] Findings of this thesis (**Chapters 6 and 7**) underscore this need. For both clinical practice and research, it is crucial to assess broader domains of disease burden, including anxiety, depression, and socio-occupational impairments, alongside attack frequency.

### *Novel pharmacological and neuromodulatory approaches*

Although the exact pathophysiology of cluster headache remains unknown, recent advances have identified several potential therapeutic targets, which will be discussed below.

### *"Illicit" drugs as therapeutics*

Data on illicit drug use (**Chapter 3**) were limited to lifetime use, preventing detailed reporting on patterns of illicit drug use. The SUPPLEMENT survey was designed to fill these gaps, examining recent use, dosing patterns, and perceived efficacy for both abortive and preventive purposes. Beyond documenting current drug use, studies to objectively assess efficacy are needed. While self-reported efficacy of psychedelics seems promising, RCTs are scarce. A small exploratory RCT psilocybin showed a reduction in attack frequency (–3.2 vs. 0.03 for placebo) that was not statistically significant, likely due to limited power.[111] Adequately powered RCTs are needed to establish whether psilocybin is indeed effective or whether previous reports reflect placebo responses.

Fortunately, more robust evidence is in the pipeline for LSD and sodium oxybate (GHB). The *LICIT RCT* (*NL-OMON57258*) is currently investigating the efficacy and safety of minidosing LSD (25 µg every three days, non-hallucinogenic) in cluster headache. Moreover, the *SUNCET RCT* will assess low-dose sodium oxybate for nocturnal cluster headache. Despite controversy surrounding the therapeutic use of "illicit" drugs, such trials are urgently needed: not only to provide novel treatments for refractory patients but also to ensure that, if effective, medications become safely and reliably available through medical channels. Conversely, if trials demonstrate inefficacy, this evidence is equally crucial to prevent patients from exposing themselves to potentially harmful or ineffective substances.

### *Hormonal replacement therapy*

The identified hypogonadism in **Chapter 5** highlights that clinicians should remain alert to possible (central) hypogonadism in cluster headache patients, especially

given the nonspecific nature of androgen deficiency symptoms. Additionally it raises the question of the potential therapeutic effects of hormonal replacement therapies (e.g., testosterone supplementation) in subgroups with hypogonadism. A small open-label study where patients with (borderline) low testosterone received testosterone suppletion showed promising results where 4/7 chronic cluster headache patients achieved remission.[112] However, results should be replicated in patients with biochemically confirmed hypogonadism.

## Greater occipital nerve (GON) modulation

Although new evidence has emerged on GON modulation in episodic cluster headache, questions remain about the application of repeated GON modulations in cluster headache. GON infiltration also appears an efficient therapy in the chronic subtype, which was confirmed in **Chapter 9**.[113] Current guidelines recommend repeating GON infiltration once every three months as maximum, but efficacy often lasts less, leaving patients undertreated.[113] Therefore, the *REGON RCT* (*NL-OMON56462*) investigates the safety and efficacy of repeated injections at a minimum 4-week interval, including adverse events, sustained response, and the effect of a second infiltration if the first fails. Upon completion, findings could inform current guidelines by providing practical recommendations for optimizing repeated GON infiltrations. Formal investigation is also warranted for bilateral GON injections in patients who experience a side-shift, as well as for other modalities such as pulsed radiofrequency.

### *Pituitary adenylate cyclase-activating peptide as a novel target*

Following the disappointing results of CGRP-antagonist, the focus has shifted to pituitary adenylate cyclase-activating peptide (PACAP) in cluster headache. This vasoactive neuropeptide is involved in the trigeminal autonomic reflex, but it also has an important role in the hypothalamus.[114] Recent provocation studies have shown that PACAP is able to trigger a cluster headache attack.[115, 116] Future studies should focus on whether PACAP antagonists (*e.g. Lu AG09222*), could potentially be efficient in cluster headache.[117]

### *Lifestyle interventions: smoking cessation*

**Chapter 2** highlighted the potential importance of smoking cessation. While quitting smoking may ameliorate cluster headache, prospective studies are needed to confirm effects and time course. Meanwhile, clinicians should encourage patients to quit smoking, while providing realistic expectations (no immediate relief but potential effect after years) and structured support through smoking cessation programs. Patients should also be informed about the risks of secondhand smoke, particularly for their children, who already carry a relatively increased genetic risk of developing cluster headache.

## 4. Psychological adaption

In addition to preventing symptoms, equal attention should be directed towards helping patients cope with the symptoms that remain. Achieving complete attack freedom is rare, particularly in chronic cluster headache. This is especially pressing for the 10–20% of patients with refractory chronic cluster headache, for whom no current medication provides sufficient relief. While pharmacological strategies remain central to both acute and preventive management, comprehensive approaches that address the broader implications of living with cluster headache are still lacking. Therefore novel interventions focusing on enhancing QoL are needed to help patients navigate the impact of their cluster headache more smoothly (Figure 9).

A first step toward comprehensive approaches that address the broader impact of living with cluster headache is the routine integration of QoL measurements in outpatient care. This provides a clearer understanding of individual disease burden and identifies patients who would benefit from additional coping tools. Subsequently, targeted interventions, such as coping strategies and psychosocial support, can be offered to improve QoL for these patients. However, evidence remains limited on which interventions are most effective and how to implement them in practice.

In line with this, the INSIGHT project is developed, which aims to identify unmet needs and subsequently establish consensus-based recommendations for implementing multidisciplinary (para)medical care in cluster headache. The project first explores these unmet needs by examining what is currently used, desired, and valued by patients. It then seeks consensus on suitable QoL interventions, spanning a broad range of approaches such as cognitive behavioural therapy (CBT), third-wave behavioural therapies (e.g., Acceptance and Commitment Therapy [ACT]), rehabilitation programs, and other paramedical interventions).[118] Finally, the project considers how these interventions could be implemented and which providers could play a role in their delivery. The results of this project should inform the development of cluster-specific QoL interventions, which could then be evaluated in prospective studies. Ultimately, after efficacy of these interventions has been established, they can be integrated into national guidelines and routine care.

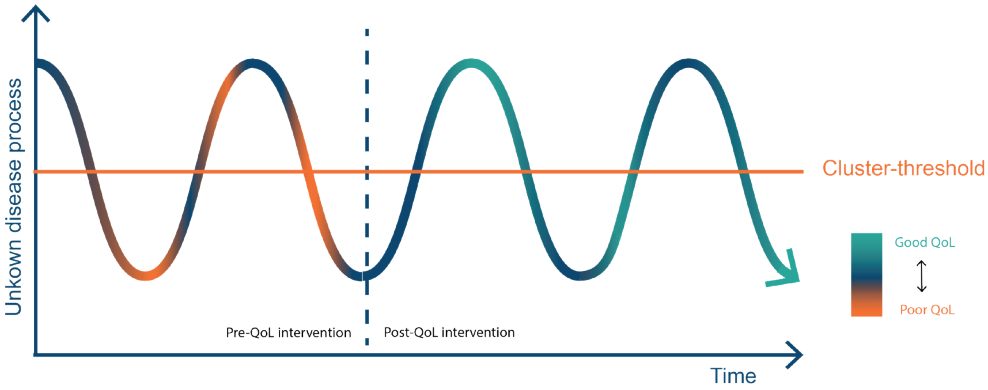


**Figure 9. Targetting Quality of Life.**

The dips and peaks of the fluctuating disease activity in cluster headache do not necessarily coincide with the lowest (depicted in orange) or the highest reported quality of life (depicted in turquoise). To improve psychological adaption, novel interventions focusing on enhancing quality of life (QoL) are needed to enable patients to better navigate their waves.

# CONCLUSION
## NAVIGATING THE WAVES

After summarizing the findings of this thesis, future directions were suggested for each of the four domains, pathophysiology, prognosis, prevention, and psychological adaptation. These domains are closely interconnected: insights gained from exploring pathophysiological mechanisms provide leads for effective interventions to break the waves, and vice versa. Future research should focus on advancing all four domains, providing a framework to enhance the ability of patients to navigate the waves of cluster headache (Figure 10).

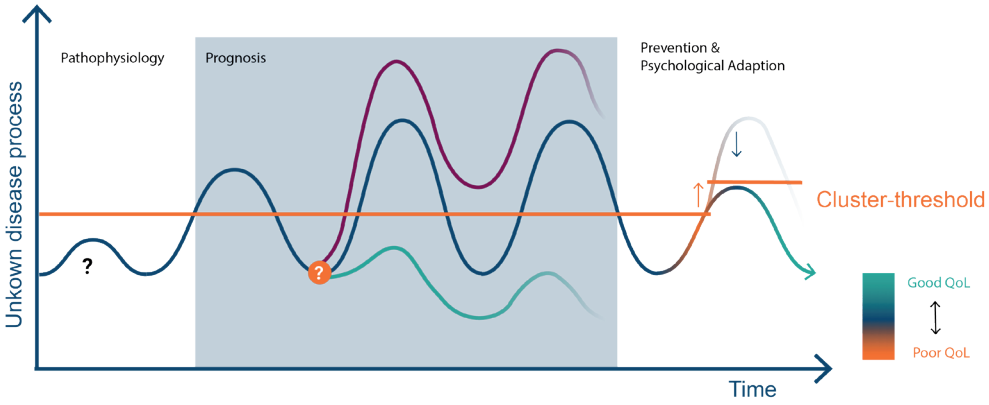


**Figure 10. Research targets to improve future navigation of the waves.**

Four interrelated domains that can be targeted towards better navigation of the waves of cluster headache: pathophysiology (understanding of disease mechanism), prognosis (prediction disease activity), prevention (reducing disease activity) and psychological adaption (empower patient's coping).

Future research on cluster headache will remain challenging but rewarding. As researchers, we must prioritize hypothesis-driven studies over readily conducted exploratory research, keeping the ultimate aim of uncovering the underlying cause of cluster headache in sight. Cluster headache is a complex, multifactorial disorder that demands a comprehensive, multifaceted approach. Integrating insights across multiple levels is essential, combining global data, multidimensional biological layers, complementary models, and diverse research disciplines, with standardized data collection and precise metadata to ensure comparability and reliability. Progress in each domain—pathophysiology, prognosis, prevention, and psychological adaptation— should also be integrated, allowing advances in one area to strengthen developments in the others. While uncovering the pathophysiology remains the long-term objective, continued progress across all four domains is essential in the interim to improve current patient care.

In conclusion, navigating the waves of cluster headache remains challenging, yet this thesis provides new insights to guide future research and clinical practice. Successful navigation requires physicians and researchers to recognize the shifting patterns of the waves and to equip patients with the necessary tools and knowledge to manage them. The findings and recommendations of this thesis aim to support this shared journey, where patients, guided by physicians and researchers, are empowered to navigate their stormy waves of cluster headache, charting a smoother course toward calmer waters.

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