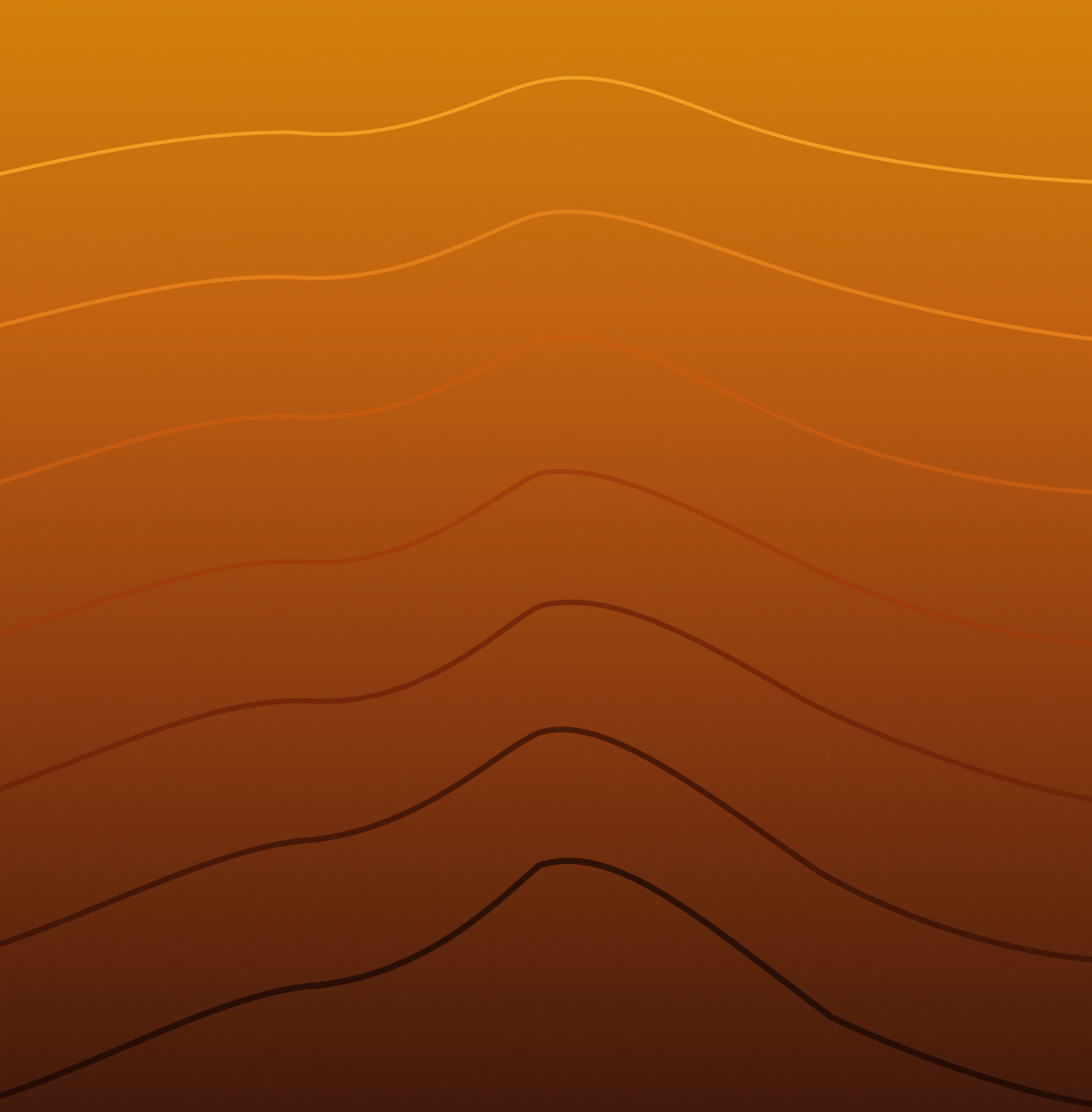


Beyond the Blister

Cannabinoids for pain in epidermolysis bullosa

Nicholas H. B. Schräder

STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT

Beyond the Blister: Cannabinoids for pain in epidermolysis bullosa

1. The predominance of pain "unpleasantness" across all EB subtypes reveals an affective dimension that nociception-focused treatments are unlikely to fully address.

   - This thesis

2. Asking patients what they need, then measuring something else, is not a methodological preference. It is a scientific error and an ethical failure.

   - This thesis

3. Pain that persists long after the wound has healed is no longer a skin disease - it is a disease with its own clinical course.

   - This thesis

4. In EB, pain is the highest-ranked patient need and a therapeutic target amenable to intervention today. What has been missing is not the will to treat, but the precision to target

   - This thesis

5. Clinically supervised sublingual cannabinoid therapy is safe and well tolerated in adults with EB. Safety concerns should not stand in the way of its clinical or experimental consideration.

   - This thesis

6. Effective pain care is both palliative and preventive.

   - This thesis

7. No man should escape our universities without knowing how little he knows.

   - J. Robert Oppenheimer

8. One good thing about music, when it hits you, you feel no pain.

   - Bob Marley

9. In the midst of chaos, there is also opportunity.

   - Sun Tzu, The Art of War (~500 BC)

Beyond the Blister:
Cannabinoids for pain in epidermolysis bullosa

Nicholas Harmannus Bernard Schräder

Beyond the Blister: Cannabinoids for pain in epidermolysis bullosa
PhD thesis, University of Groningen, the Netherlands

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The research described in this thesis was carried out at the Department of Dermatology, UMCG Center of Expertise for Blistering Diseases, and at the Anaesthesiology Pain Centre, University Medical Center Groningen, University of Groningen, the Netherlands.

The research was financially supported by DEBRA UK. Felix Farma B.V., The Hague, supplied the investigational medicinal product and matched placebo for the C4EB trial. Neither party was involved in the design, conduct, analysis or reporting of the studies.

Cover design and chapter openers: N.H.B. Schräder
Layout and printing: ProefschriftMaken, www.proefschriftmaken.nl

ISBN (printed): 978-94-653-4665-6

university of groningen

Beyond the Blister:

Cannabinoids for pain in epidermolysis bullosa

PhD thesis

to obtain the degree of PhD of the
University of Groningen
on the authority of the
Rector Magnificus Prof. J.M.A. Scherpen
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

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To

Dr. H.F.J. Schräder †

A father and physician, whose quiet attention to patients preceded every lesson in medicine.

and

Prof. dr. M.F. Jonkman †

Mentor and colleague,
whose candour was his greatest kindness.

LIST OF ABBREVIATIONS

AAPT	Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks – American Pain Society Pain Taxonomy
ACC	Anterior Cingulate Cortex
AE	Adverse Event
AVG	Algemene Verordening Gegevensbescherming (Dutch General Data Protection Regulation / GDPR)
BOLD	Blood-Oxygen-Level-Dependent
C4EB	Cannabinoids for Epidermolysis Bullosa (randomised controlled trial)
CB1	Cannabinoid Receptor Type 1
CB2	Cannabinoid Receptor Type 2
CBD	Cannabidiol
CBM	Cannabinoid-Based Medicine
CBME	Cannabis-Based Medicine Extract
CBT	Cognitive Behavioural Therapy
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
COSEB	Core Outcome Set for Epidermolysis Bullosa
CS	Central Sensitisation
CSI	Central Sensitisation Inventory
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
DDEB	Dominant Dystrophic Epidermolysis Bullosa
DEB	Dystrophic Epidermolysis Bullosa
DEBRA	Dystrophic Epidermolysis Bullosa Research Association
DFNS	German Research Network on Neuropathic Pain (Deutsche Forschungsverbund Neuropathischer Schmerz)
DLQI	Dermatology Life Quality Index
DMN	Default Mode Network
DN-4	Douleur Neuropathique 4

DSMB	Data Safety Monitoring Board
EB	Epidermolysis Bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis Bullosa Simplex
ECS	Endocannabinoid System
ER	Extended Release
fMRI	Functional Magnetic Resonance Imaging
HADS	Hospital Anxiety and Depression Scale
HADS-D	Hospital Anxiety and Depression Scale – Depression Subscale
HRQOL	Health-Related Quality of Life
IENFD	Intraepidermal Nerve Fibre Density
IMP	Investigational Medicinal Product
IQR	Interquartile Range
IR	Immediate Release
JEB	Junctional Epidermolysis Bullosa
MCID	Minimal Clinically Important Difference
ME-ICA	Multi-Echo Independent Component Analysis
MRI	Magnetic Resonance Imaging
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NGF	Nerve Growth Factor
NIH	National Institutes of Health
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
N_2O	Nitrous Oxide
PBI	Patient Benefit Index
PBI-S	Patient Benefit Index – Standard Version
PBQ	Patient Benefit Questionnaire
PCS	Pain Catastrophizing Scale

PEBLES	Prospective Epidermolysis Bullosa Longitudinal Evaluation Study
PNQ	Patient Needs Questionnaire
PQAS	Pain Quality Assessment Scale
PSEQ	Pain Self-Efficacy Questionnaire
QOLEB	Quality of Life in Epidermolysis Bullosa
QST	Quantitative Sensory Testing
RCT	Randomised Controlled Trial
RDEB	Recessive Dystrophic Epidermolysis Bullosa
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SF-MPQ-2	Short-Form McGill Pain Questionnaire – 2
SPSS	Statistical Package for the Social Sciences
THC	Δ9-Tetrahydrocannabinol
TRP	Transient Receptor Potential
UMCG	University Medical Centre Groningen
VAS	Visual Analogue Scale

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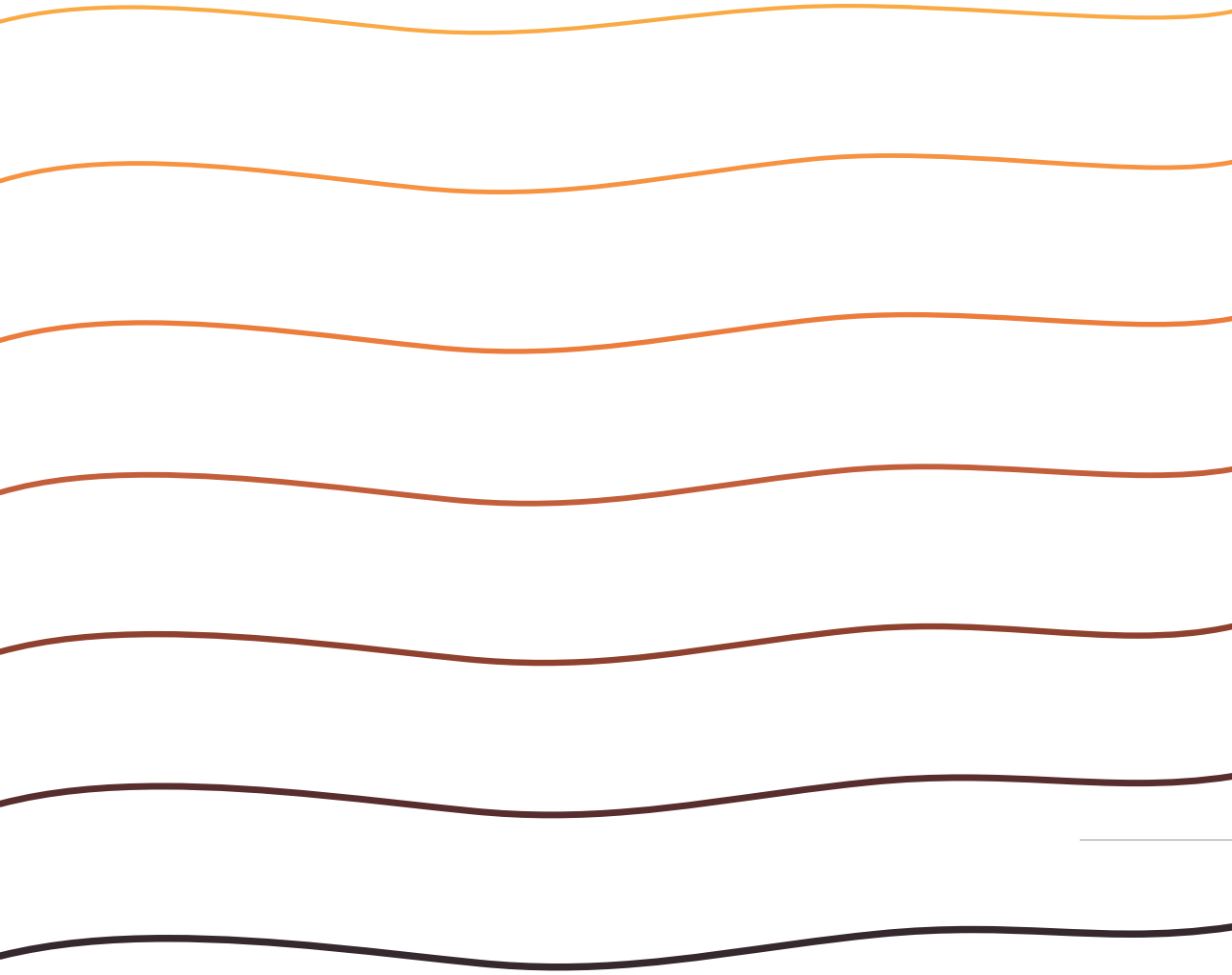
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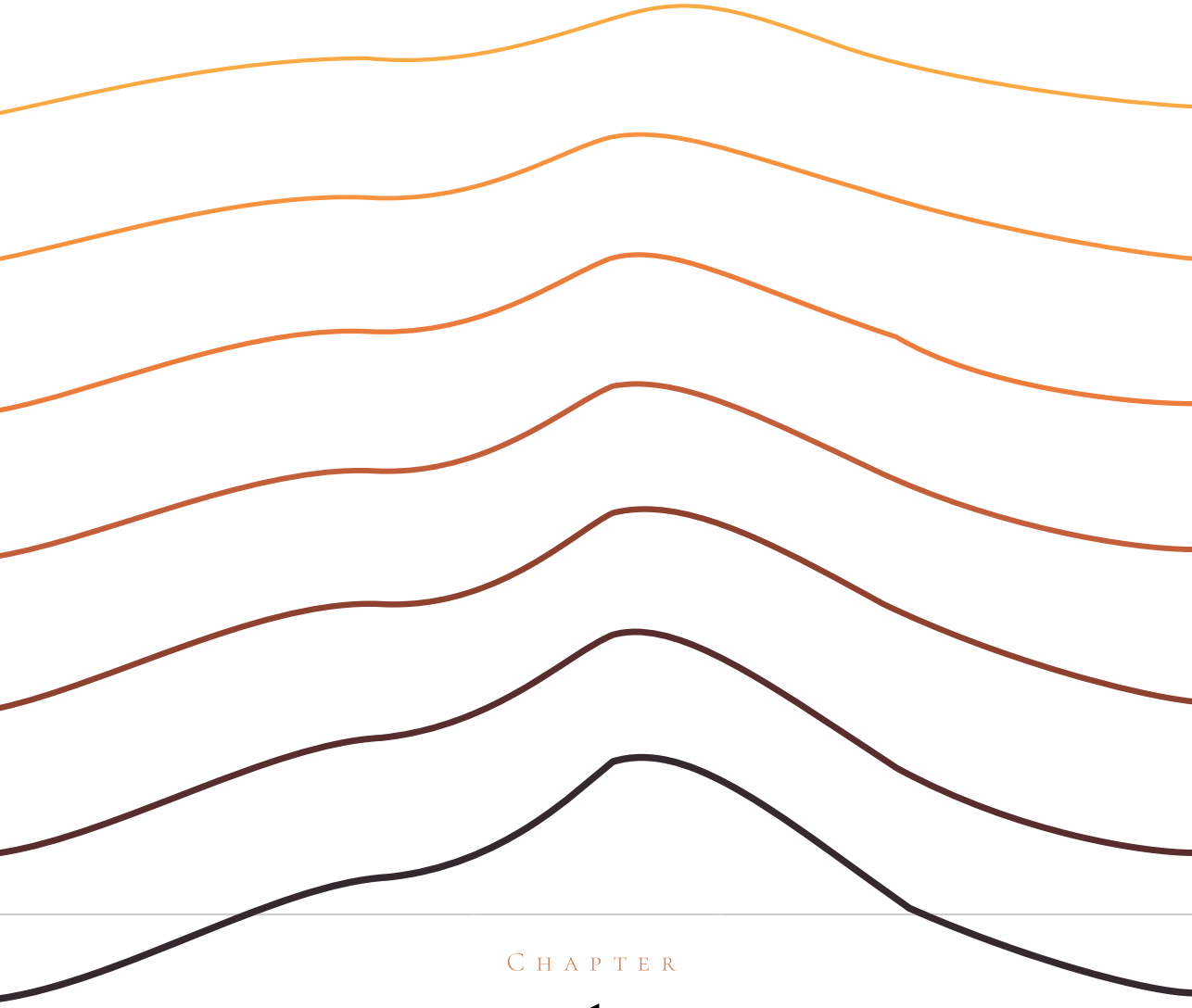
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CHAPTER

1

General Introduction

EPIDERMOLYSIS BULLOSA

Background and clinical features

It was more than a century ago in 1870 when prominent Viennese dermatologist Ferdinand Ritter von Hebra proclaimed the existence of a hereditary blistering skin condition, and not long afterwards when the term Epidermolysis Bullosa (EB) (Latin for: *skin separation with blisters*) was coined by British paediatrician Edward Alfred Cockayne [56]. Since then, EB research has unveiled a group of inheritable blistering disorders primarily affecting, but not limited to, the skin and mucous membranes, leading to pain and itch often on a daily basis [38]. EB is an orphan disease with a point-prevalence of 22.4 per million population, or roughly 464 living patients in the Netherlands; this is likely an underestimation with true prevalence at around 600 [7]. Rigorous data collection and registry input by expertise centres around the world are key to collating important epidemiological data on EB. The University Medical Centre of Groningen hosts the European Reference Network centre and national registry for blistering diseases, providing interdisciplinary care to the four major types: EB Simplex (EBS), Junctional EB (JEB), Kindler EB and Dystrophic EB (DEB), the last clinically subdivided into recessive DEB (RDEB) and dominant DEB (DDEB) [38].

Understanding the clinical presentations of EB types requires recognising the reduced resilience of the skin and mucous membranes to mechanical stress. At the molecular level, the absence, significant reduction, or aberrant presence of structural extra-, inter-, and intracellular proteins leads to splaying of epidermal cells or separation, for example, at the dermo-epidermal junction [46]. Clinically, these defects are observed as blisters or erosions of the skin or mucous membranes. However, the degree to which proteins in the integument are affected, by way of novel or inherited pathogenic DNA mutations, along with their anatomical localisations, further delineates the EB types.

EBS, the most common form of EB, is primarily characterised by cleavage within basal keratinocytes and encompasses a wide spectrum of clinical severity, ranging from mild, localised blistering or keratoderma of non-hairy (glabrous) skin to more severe forms involving generalised blistering and wounds in the neonatal phase, and can be lethal. Depending on the protein affected, other organs may be involved as well, such as dilated cardiomyopathy due to pathogenic variations in Kelch-like family member 24 (KLHL24) [98]. EBS patients are particularly affected

in warm, humid weather owing to an increased aggregation of defective cytoskeletal proteins in these environments [96].

JEB is characterised by blistering that occurs at the level of the lamina lucida within the cutaneous basement membrane zone (BMZ) and has two main subtypes: intermediate and severe [27]. In JEB, the affected proteins are also present in other systems such as the genitourinary, respiratory, and digestive tracts, leading to a range of potential complications in these organ systems. Severely disrupted wound healing plays a central role. Severe JEB is lethal in infancy, with an average life expectancy of 5.8 months (range 0.5-32.6 months) [99].

DDEB and RDEB both exhibit pathology involving type VII collagen and present with skin cleavage at the level of the lamina densa [2]. RDEB has more pronounced clinical manifestations than DDEB, which is often limited to secondary skin changes and excessive pruritus (often classified as DDEB-pruriginous type). Distinctive features of RDEB include scar tissue formation such as seen in mitten hand deformities, corneal abrasions, oesophageal strictures, and aggressive skin cancer formation [4,18,51,67].

Lastly, Kindler EB is the rarest EB type (<1% of cases) and results from pathogenic variants in the intracellular protein kindlin 1 [47]. Kindler EB is characterised by progressive poikiloderma and prominent mucous membrane involvement.

Only recently were the first two targeted, non-permanent gene therapies granted marketing authorisation in Europe and the United States for patients with DEB, but despite these promising efforts, such treatments remain inaccessible to most EB patients [13,42,74,79,82,91].

Beyond the Blister

Although EB is conventionally described as a mechano-bullous disease, focusing solely on mechanical disruption does not explain the full spectrum of clinical features observed. Besides their crucial role in maintaining tissue integrity, the structural proteins disrupted in EB also participate in complex intra- and extracellular signalling processes [14].

This dysregulation inherent to EB unremittingly affects homeostasis, leading to epigenetic changes as well as disrupted metabolic and neuronal signalling [95]. Example patho-mechanisms include the persistent

chronic wounds, chronic bacterial colonisation, extreme scarring, vast tissue and systemic inflammation, anaemia, microbial dysbiosis, skin cancer and lastly refractory symptoms like pain and pruritus, which are often disproportionate to underlying measurable tissue damage.

The unfortunate result is a heterogeneous clinical picture and disease experience with significant variability between patients and within patients over the disease course, even before accounting for environmental, lifestyle and iatrogenic factors [24,59–61,77,85]. Consequently, clinical management in EB adopts a pragmatic or empirical approach. It focuses on prevention and symptom management, drawing on knowledge from other dermatological and pain conditions, with individual patient needs increasingly incorporated into care plans [39].

Clinical studies in EB have frequently failed to translate into effective treatments; conversely, promising empirical therapies have often been unsuccessful in research settings, leaving patients to their own forms of trial and error [68]. It is therefore important to bridge the scientific gap between emerging patient needs and the valuable pool of patient discoveries, in order to generate meaningful progress in this clinical field [1,11,21,35,73,90].

Research has repeatedly concluded that aside from wound care, effective pain treatment is among the most significant, if not the most significant, unmet need in the management of EB [12,21,44,81,83,86–88,100]. It is the collation of patient needs and experiences that has driven the research presented in this thesis.

Patient-centred outcome research in EB

Rare diseases present challenges for outcome research. Small patient populations, phenotypic heterogeneity and the absence of validated disease-specific instruments have historically limited the quality of clinical evidence. Meaningful progress requires moving beyond surrogate endpoints towards outcomes that reflect what matters most to patients, a principle central to patient-centred outcome research [6,63,73].

PAIN IN EPIDERMOLYSIS BULLOSA

> *"...Finally, it has also been argued that pain is more than a symptom, that chronic pain may be a disease with its own clinical course..."* [75]

Pain in EB can occur from birth through end of life, and at every stage in between, and represents a major burden for patients and caregivers [12,38,39]. Large cohorts show significant pain presence in 74–87% of patients across EB types, with profound impacts on daily function, school/work, and mental health [11,12,26,32,34,84,87]. It arises from diverse aetiologies directly related to EB pathogenesis (blistering and wounds), can be secondary (scarring, infections and skin cancer) and initiated through medical procedures (dressing changes, biopsies, venepuncture and surgery), amongst others [34]. Patients with severe EB subtypes (RDEB, JEB) typically report the highest pain levels due to significant clinical features, yet pain in milder EBS and DDEB is also a prominent feature and often disproportionate to visible lesions [15,26,32,55,83].

Controlled trials evaluating pain treatments in EB are almost non-existent; management therefore relies on expert consensus, extrapolation from other conditions, and international best-practice guidelines (2014) [34,36]. These address wound pain, procedural pain, bathing, dressing changes, gastrointestinal pain, bone pain, infant pain, end-of-life care, and psychological support.

Recent "burden mapping" studies highlight that most identifiable aetiologies for pain stem from cutaneous complications including infection, chronic inflammation, dysregulated wound healing, scarring, and hypergranulation [60]. These complex, multi-directional interactions subsequently maintain a vicious cycle of underlying patho-mechanisms and persistent nociceptive input. These data provide important clues about the underlying causes of pain in EB, thereby informing potential treatment avenues. The main mechanisms of pain in EB are as follows:

Nociceptive Pain

Nociceptive pain is *pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors* [49]. Nociceptive pain predominates in EB and manifests as acute pain from spontaneous or friction-induced blisters and inflammation, as well as chronic pain from non-healing wounds, infection, defective remodelling leading to retractile scarring and hypergranulation, amongst others. In severe types

such as RDEB and JEB, pain even stems from cutaneous squamous cell carcinoma, oesophageal strictures with painful dysphagia, and severe constipation with perianal blistering or fissures [18,62,65]. Management involves prevention, optimising wound healing, itch control to reduce traumatic scratching, and analgesia following best-practice guidelines, including paracetamol and NSAIDs for mild pain and the complete hierarchy of opioids for moderate-to-severe pain [22,34,72]

Procedural & Iatrogenic Pain

Procedural and iatrogenic pain in EB consists of acute nociceptive pain triggered by medical interventions and daily care [34]. Dressing changes remain the most well-known and frequent event in EB due to adherent wound exudate, temperature and moisture shifts, and re-wounding [12]. Additionally, pain intensity may be amplified by anticipatory anxiety, or catastrophising, especially in children [57,76]. Other procedures include venepuncture, biopsies, surgery and oesophageal dilatation. Management comprises short-acting analgesics or, for severe cases, sedation and general anaesthesia. Dissociative drugs such as ketamine have been reported to be effective in case studies [80]. Other techniques involve soaking dressings in baths with bleach or salt to reduce bacterial load, topical anaesthetics, pre-procedural non-adhesive dressing techniques, anxiety reduction through anxiolytics, distraction, hypnosis, cognitive-behavioural therapy and environmental optimisation [3,34,70].

Neuropathic Pain

Neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system [49]. Several studies have established small fibre neuropathies in patients with RDEB, evidenced by dysfunctional cutaneous sensory signalling, reduced intraepidermal nerve fibre density, and aberrant dermal architecture [8,9,16,51]. Neuropathies are clinically suspected in other EB subtypes due to burning, shooting, or electric-type pain that is often refractory to standard analgesics. Recent studies have suggested pregabalin may offer effective neuropathic pain management in EB [9].

Nociplastic Pain

Nociplastic pain is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, or evidence for disease or lesion of the somatosensory system causing the pain [49]. It is important to note that central sensitisation, the amplification of neural signalling within the

central nervous system, represents one of several neurobiological mechanisms that may underlie nociplastic pain, but is not synonymous with it as a clinical category. Central sensitisation can also occur in the context of nociceptive and neuropathic pain states.

As pain in EB cannot be fully accounted for by nociceptive or neuropathic mechanisms alone, nociplastic phenomena may contribute to the disproportionate pain observed in milder EB subtypes, pain occurring in apparently healthy skin, and could explain the limited effectiveness of conventional analgesics in EB in general. Additional factors predisposing to this pain mechanism include widespread acute-on-chronic pain phenomena such as recurring wounds, peri-procedural anxiety and neuro-immuno-cutaneous dysregulation, as well as somatic symptom disorder, which may play an amplifying or maintaining role [34,44,54,76,94].

Pain Summary

In summary, pain in EB is characteristically heterogeneous, with nociceptive, neuropathic and nociplastic components frequently coexisting in the same patient. Each mechanism involves distinct pathophysiological processes and therefore requires targeted strategies ***(figure 1)***. Nociceptive pain is addressed through optimised wound management and conventional analgesics, whereas neuropathic elements may respond to targeted pharmacotherapy, including pregabalin. By contrast, no interventions have yet been specifically designed or clinically evaluated for the nociplastic pain dimensions in EB. Despite advances in the mechanistic understanding of pain in EB, it remains inadequately controlled, underscoring a pressing unmet need for novel approaches, whereby understanding nociplastic mechanisms provides a new outlook. Furthermore, the clinical coexistence of nociceptive, neuropathic and nociplastic mechanisms constitutes a mixed pain state, a concept central to understanding the complexity of pain in EB and to rationalising multimodal treatment approaches. One such approach gaining increasing attention in chronic pain conditions is the use of cannabinoid-based medicines (CBM).

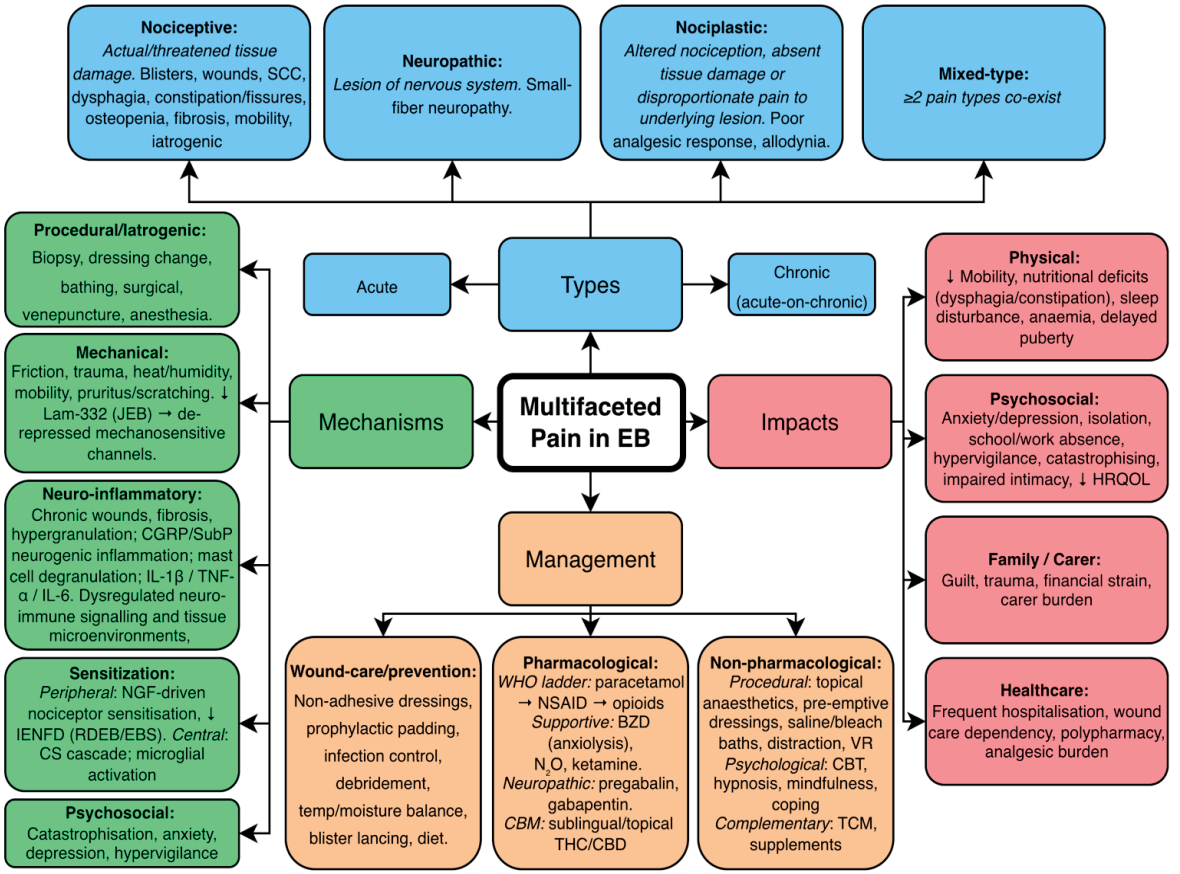

Nociceptive:
Actual/threatened tissue damage. Blisters, wounds, SCC, dysphagia, constipation/fissures, osteopenia, fibrosis, mobility, iatrogenic
Neuropathic:
Lesion of nervous system. Small-fiber neuropathy.
Nociplastic:
Altered nociception, absent tissue damage or disproportionate pain to underlying lesion. Poor analgesic response, allodynia.
Mixed-type:
≥2 pain types co-exist
Procedural/Iatrogenic:
Biopsy, dressing change, bathing, surgical, venepuncture, anesthesia.
Mechanical:
Friction, trauma, heat/humidity, mobility, pruritus/scratching. ↓ Lam-332 (JEB) → de-repressed mechanosensitive channels.
Neuro-inflammatory:
Chronic wounds, fibrosis, hypergranulation; CGRP/SubP neurogenic inflammation; mast cell degranulation; IL-1β / TNF-α / IL-6. Dysregulated neuro-immune signalling and tissue microenvironments,
Sensitization:
Peripheral: NGF-driven nociceptor sensitisation, ↓ IENFD (RDEB/EBS). Central: CS cascade; microglial activation
Psychosocial:
Catastrophisation, anxiety, depression, hypervigilance
Acute
Types
Chronic (acute-on-chronic)
Mechanisms
Multifaceted Pain in EB
Impacts
Management
Wound-care/prevention:
Non-adhesive dressings, prophylactic padding, infection control, debridement, temp/moisture balance, blister lancing, diet.
Pharmacological:
WHO ladder: paracetamol → NSAID → opioids
Supportive: BZD (anxiolysis), N_2O, ketamine.
Neuropathic: pregabalin, gabapentin.
CBM: sublingual/topical THC/CBD
Non-pharmacological:
Procedural: topical anaesthetics, pre-emptive dressings, saline/bleach baths, distraction, VR
Psychological: CBT, hypnosis, mindfulness, coping
Complementary: TCM, supplements
Physical:
↓ Mobility, nutritional deficits (dysphagia/constipation), sleep disturbance, anaemia, delayed puberty
Psychosocial:
Anxiety/depression, isolation, school/work absence, hypervigilance, catastrophising, impaired intimacy, ↓ HRQOL
Family / Carer:
Guilt, trauma, financial strain, carer burden
Healthcare:
Frequent hospitalisation, wound care dependency, polypharmacy, analgesic burden

Figure 1: Pain in Epidermolysis Bullosa (EB) is multifaceted, arising from the interplay of distinct pain types, underlying mechanisms, broad impacts, and a range of management strategies [34]. Four pain types are recognised: nociceptive pain, driven by actual or threatened tissue damage; neuropathic pain, arising from lesions of the somatosensory nervous system, including small-fibre neuropathy [9,16]; nociplastic pain, characterised by altered nociception in the absence of identifiable tissue or nerve damage [45], manifesting as disproportionate pain, allodynia, and poor analgesic response; and a mixed-type, in which two or more pain types coexist. Pain may present as acute, chronic, or the clinically common acute-on-chronic pattern. Underlying mechanisms span procedural and iatrogenic triggers [10,43], mechanical factors — including the loss of laminin-332 in JEB [17], which de-represses mechanosensitive channels — neuro-inflammatory cascades and dysregulated neuro-immune tissue microenvironments [52,66,89], peripheral and central sensitisation, and psychosocial contributors. The impacts of pain extend beyond the physical domain to encompass psychosocial wellbeing [29,30], health-related quality of life [31,100], family and carer burden [12], and significant healthcare utilisation. Management is organised across three domains: wound care and prevention [22,72], pharmacological approaches [64,80] including cannabinoid-based medicines, and non-pharmacological strategies encompassing procedural, psychological [54], and complementary interventions [69]. This overview is detailed but not exhaustive; new and developing curative therapies are not included.

Abbreviations: BZD, benzodiazepine; CBM, cannabinoid-based medicine; CBD, cannabidiol; CBT, cognitive behavioural therapy; CGRP, calcitonin gene-related peptide; CS, central sensitisation; EB, epidermolysis bullosa; EBS, EB Simplex; HRQOL, health-related quality of life; IENFD, intraepidermal nerve fibre density; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JEB, Junctional EB; Lam-332, laminin-332; N_2O, nitrous oxide; NGF, nerve growth factor; NSAID, non-steroidal anti-inflammatory drug; RDEB, Recessive Dystrophic EB; SCC, squamous cell carcinoma; SubP, substance P; TCM, traditional Chinese medicine; THC, tetrahydrocannabinol; TNF-α, tumour necrosis factor-alpha; VR, virtual reality; WHO, World Health Organization.

CANNABINOID-BASED MEDICINES

The use of CBMs dates back millennia [20]. Recent research has renewed interest by highlighting the human endocannabinoid system (ECS), a neuro-modulatory network comprising receptors, endogenous ligands and their metabolic enzymes [20]. The ECS maintains homeostasis across the nervous, immune and cutaneous systems, regulating synaptic plasticity, neuroprotection, inflammation, mood, metabolic balance and sensory processing [58,97].

Cannabinoid receptors *CB1* and *CB2* are widely expressed throughout the central and peripheral nervous systems, predominantly on presynaptic terminals. Their activation inhibits voltage-gated calcium channels, resulting in suppression of excitatory and inhibitory neurotransmitter release, including glutamate, GABA, noradrenaline, dopamine, serotonin, acetylcholine and substance P [53]. Importantly, *CB1* expression is minimal in brainstem cardiorespiratory centres, conferring a substantially lower risk of fatal respiratory depression compared with opioids [40,50].

Dysregulation of the ECS is implicated in numerous conditions, including nerve injury, chronic inflammation and skin disorders [19,33]. In skin, the ECS modulates keratinocyte proliferation, immune responses, fibrosis and sensory phenomena including both pain and pruritus. The ECS can be targeted pharmacologically by cannabinoid-based medicines (CBMs). Over 100 plant-derived phytocannabinoids have been identified, with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most well studied [25]. These CBMs target the ECS, offering potential therapeutic avenues for neurological, inflammatory and dermatological conditions characterised by pain and dysregulated tissue microenvironments [23,78].

Of particular interest are the immunomodulatory effects of CBMs. For example, cannabinoid receptor agonism has been shown to produce analgesic effects in pain arising from nerve injury and inflammation [53]. Cannabinoids also have the capability to attenuate cutaneous neurogenic inflammation by inhibiting the release of Calcitonin Gene-Related Peptide (CGRP) [78]. Microglia rapidly activate in response to nervous system injury or inflammation whereby a hallmark of this activation is marked upregulation of *CB2* receptors. Selective *CB2* agonism has been shown to suppress microglial release of pro-inflammatory mediators and

limits neuroinflammation, thereby attenuating central sensitisation and reducing both neuropathic and nociplastic pain [5,37,41,93].

Most importantly, mechanisms of action of CBMs demonstrate beneficial modulation of central sensory processing, such as in chronic pain states. A study of capsaicin-induced pain and hyperalgesia demonstrated analgesic effects of THC on pain unpleasantness, without changes in overall pain intensity [48]. This effect correlated with a reduction in functional connectivity within the ACC and increased connectivity within the right amygdala. Activity in both the ACC and the amygdala underpins the negative affective states associated with chronic pain [71,92]. In addition to effects on pain signalling mechanisms, ECS modulation through CBMs has been shown to attenuate anxiety, catastrophising, hypervigilance and sleep disturbances [28].

Taken together, these properties support the rationale for a potential therapeutic strategy for pain treatment by way of CBM administration in EB.

GENERAL AIMS

This thesis aims to investigate the therapeutic potential of cannabinoid-based medicines as a novel pharmacologic strategy for pain management in EB. A central objective was to anchor research questions in the lived experiences and perspectives of patients with EB, thereby ensuring that future therapeutic developments remain firmly rooted in patient-centred priorities and unmet needs. To this end, the research follows a sequential, patient-centred methodology: beginning with the identification and prioritisation of unmet patient needs, followed by characterisation of the dominant pain qualities in EB, an inventory of real-world CBM use through observational studies, and culminating in the design and execution of the first randomised, placebo-controlled crossover trial of sublingual CBMs in EB.

THESIS OUTLINE

In **Chapter 2**, we analysed EB patient perspectives on their general treatment needs. A two-step survey, the Patient Benefit Index, was used to assess patient needs and subsequent treatment benefits. Pain was identified as the predominant unmet need, with pain scores positively correlated with all other assessed patient needs, establishing effective pain treatment as the central therapeutic priority for patients with EB.

In **Chapter 3** we evaluated the pain qualities reported by EB patients across all EB subtypes using the Pain Quality Assessment Scale. Unpleasantness was found to be the dominant pain quality across all EB subtypes, a finding that directly informed the selection of the primary outcome measure for the C4EB trial.

In **Chapter 4** we present a case series of three EB patients using prescribed CBMs to manage pain and EB-related symptoms. CBM use was associated with reductions in pain and/or improvements in EB-related quality of life, providing clinical rationale for a controlled trial.

In **Chapter 5** we examine the use of both self-acquired and prescribed cannabinoid-based medicines in an international cohort of EB patients across all subtypes. CBM use was prevalent, with the majority of respondents reporting improvements in pain and itch, alongside a generally favourable side effect profile.

In **Chapter 6** we describe the C4EB trial protocol. The trial was a double-blind, randomised, placebo-controlled crossover study of sublingual Transvamix® (10% THC/5% CBD). Affective pain quality subscales of the short-form McGill Pain Questionnaire-2 were selected as the primary outcome, grounded in the findings of **Chapters 2-3**.

Chapter 7 presents the published C4EB trial results, and **Chapter 8** presents the unpublished secondary analyses and an extended discussion of the trial findings.

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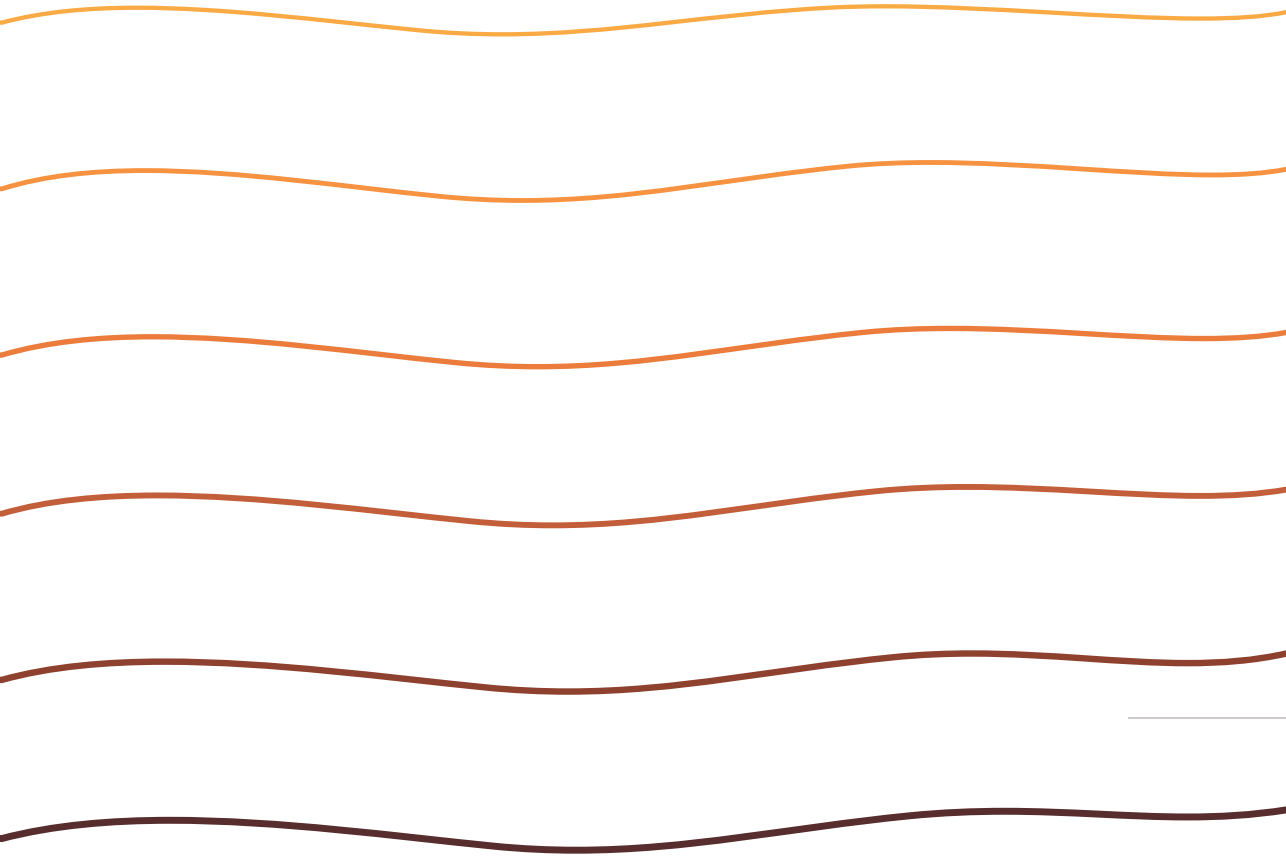
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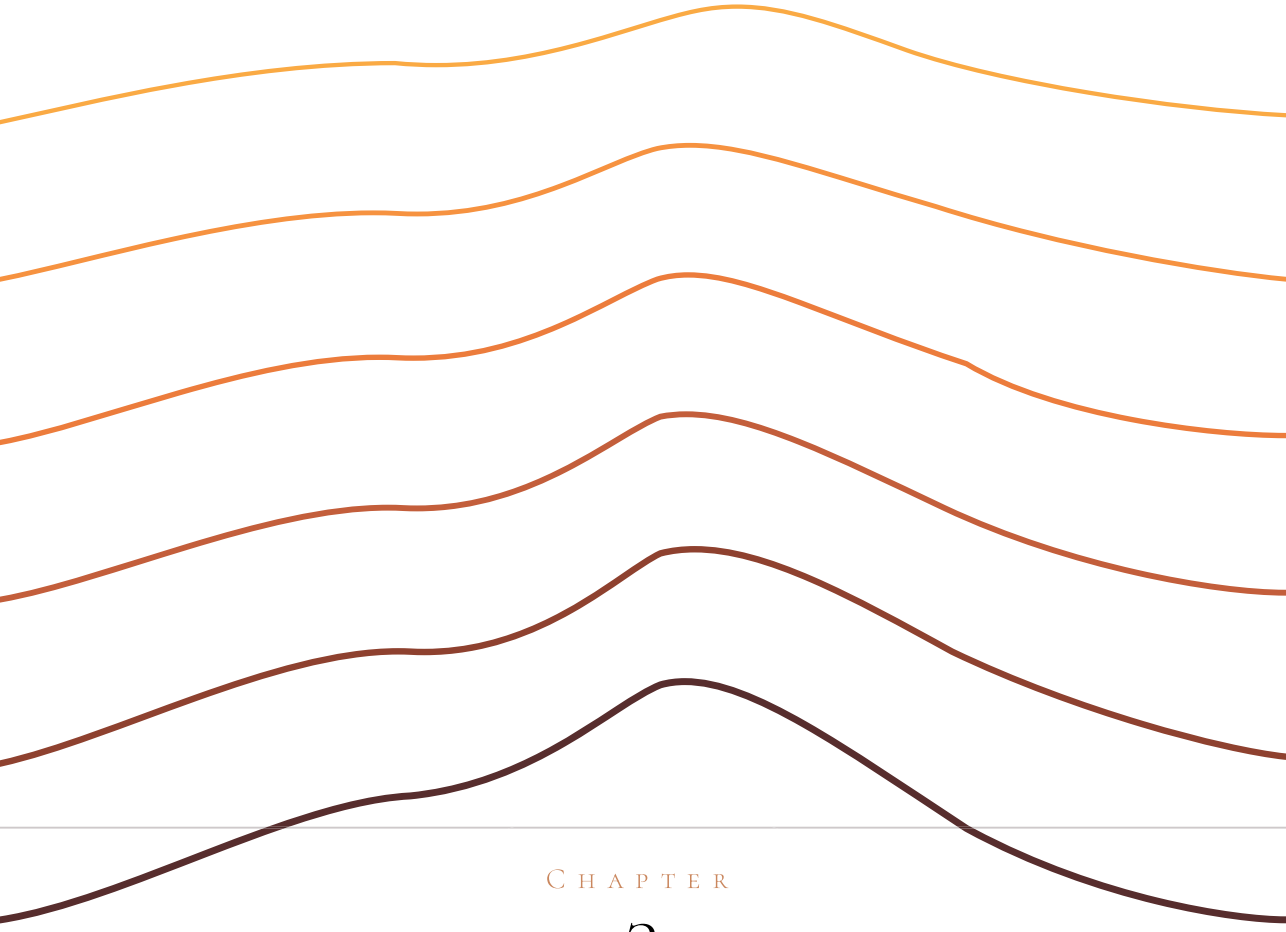
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Part I:

Patient Needs and the Burden of Pain





Chapter

2

Identifying Epidermolysis Bullosa Patient Needs and Perceived Treatment Benefits: An Explorative Study Using the Patient Benefit Index

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J Clin Med. 2021 Dec 13;10(24):5836

ABSTRACT

Epidermolysis bullosa (EB) is a genetic blistering skin condition for which no cure exists. Symptom alleviation and quality of life are therefore central to EB care. This study aimed to gain insight into EB patient needs and benefits from current clinical care. Two questionnaires were administered cross-sectionally to adult EB patients at the Dutch expertise centre for blistering diseases. Patient needs and benefits were analyzed using the patient benefit index survey (PBI-S). Ancillary data were compiled pertaining to self-reported EB severity, pain and pruritus, as well as current and previous treatments. In total, 104 participants were included (response rate 69.8%). Sixty-eight participants comprised the analyzed cohort (n = 36 omitted from analysis). The needs given the highest importance were *to get better skin quickly* (64.7%) and *to be healed of all skin alterations* (61.8%). A positive correlation between pain and EB severity and the importance of most needs was observed. Minimal clinically important differences within the PBI-S, relating to reported benefits from clinical care, were reported by 60.3% of the cohort. This study highlights a discrepancy between patient needs and feasible treatment outcomes. Utilizing the PBI-S in conjunction with well-established multidisciplinary care may catalyze the process of tailoring treatments to the needs of individual patients.

INTRODUCTION

Epidermolysis bullosa (EB) is an inherited skin condition with known variants in 16 genes and comprises a heterogenous group of clinical phenotypes. The main types are based on the level of blister formation and include EB simplex (EBS), junctional EB (JEB), dominant dystrophic EB (DDEB), recessive dystrophic EB (RDEB) and Kindler EB [28]. EB is characterised by blistering of the skin and mucous membranes, with some forms showing extracutaneous involvement, either secondary to chronic extensive wounds and scarring, or as a direct consequence of molecular defects [9,65].

Patients report significant effects on their quality of life (QoL) due to chronic symptoms, incurred treatment costs, reduced work/school productivity and low mood-states, amongst an array of factors [10,29,33,50,61,66]. Complications, such as aberrant wound healing, scarring and infection, as well as the psychosocial impact, mean that this disease is clinically challenging and requires expert multidisciplinary management.

As EB cannot be cured, numerous clinical practice guidelines are aimed at the prevention of secondary pathologies, symptom alleviation and psychosocial improvements. These are presently the most tangible elements for improving day-to-day QoL of EB patients [13,26,43,62]. In order to effectively improve outcomes and the QoL of EB patients, it is imperative that clinicians pay adequate attention to the needs in both individual patients and distinct EB types [41]. This study aimed to gain insight into EB patient needs and their reported benefits from their current EB care. Additional demographics, patient-reported characteristics, pain and pruritus treatments and recreational drug-use were taken into account.

MATERIALS AND METHODS

This was a cross-sectional study at the European Reference Network (ERN) expertise centre for blistering diseases in the University Medical Centre Groningen (UMCG) [4]. Participants had a genetic diagnosis of inherited EB, were at least 16 years old, were living in the Netherlands, could read and write in Dutch and could provide informed consent. Eligible participants were identified in the Dutch EB registry, contacted by telephone, informed about the study procedures and invited to participate

through the dispensation of a brochure and consent form. The Dutch EB registry does not discriminate between patients receiving treatment at the UMCG or other healthcare settings; therefore, the latter were excluded from analysis after data collection. The study was approved by the UMCG institutional ethics review board on 08-01-2019 (METc #201800968).

Participants were administered two surveys. Part A was a self-assembled survey on patient burden of illness and treatments, completed through a telephone interview. Burden of illness comprised self-reported EB severity (mild, moderate and severe), as well as pain and pruritus intensity throughout the previous week (numeric rating scale (NRS): 0–10 for morning, afternoon and evening). Participants reported prescribed pharmacologic pain and pruritus treatments, used at the time of survey completion. Systemic pharmacologic treatments that were previously prescribed were reported using a multiple-choice list based on systemic therapies from best practice EB guidelines. Lastly, recreational drug-use (tobacco, alcohol, cannabis and other drugs) and its effects on EB were reported. Responses were categorized during post-hoc analysis.

Part B consisted of the validated patient benefit index survey (PBI-S), standard version, completed digitally by participants. The PBI-S permitted the evaluation of individual needs and benefits in the treatment of dermatologic conditions [3]. The first section was comprised of the patient needs questionnaire (PNQ). Participants rated the importance of each of the 25 statements (not at all, somewhat, moderately, quite, very and does not apply to me). The second section, the patient benefit questionnaire (PBQ), consisted of the same 25 statements. However, participants reported the extent to which the PNQ statements were achieved. In this study, participants were asked to refer to their "general EB clinical care at the UMCG". The combined PNQ and PBQ data enabled the calculation of the patient benefit index (PBI). The PBI could range from no (0) to maximum benefit (4). A PBI score ≥1 portrayed a minimal clinically important difference (MCID) after intervention, taken from PBI validation studies in other dermatologic conditions [3]. The PBI-S distinguished between 5 subscales: physical impairments, psychological impairments, social impairments, impairments due to therapy and having confidence in healing [8].

Both surveys were built into a digital outcome monitoring program (RoQua). Sociodemographic and medical data (EB type, age, sex and time since diagnosis) were obtained from the Dutch EB registry [4]. Data were

represented using descriptive statistics (frequencies and proportions for categorical data—means and standard deviations (SD), median values and interquartile ranges (IQR) for continuous data). Means comparisons were performed for normally distributed variables; otherwise, non-parametric testing was applied. Participants' needs (PNQ) were correlated using the Spearman rho correlation coefficient, with self-reported outcomes (EB severity, pain and pruritus scores) and sociodemographic data (age and time since diagnosis). Bootstrapping was performed for confidence intervals. The correlation coefficients (rs) were defined as: negligible (0–0.29), low (0.3–0.49), moderate (0.5–0.69) and high (0.7–1.0) [47]. A two-sided $p = 0.05$ was set a priori for statistically significant differences. Statistical analyses were performed using IBM SPSS Statistics (Version 23.0. Armonk, NY) and Stata Statistical Software (Release 16. College Station, TX).

RESULTS

Study Population

In total, 149 patients were contacted, of which 10 declined participation. A total of 104 participants returned either paper or electronically signed informed consent forms and completed both the PBI-S and supplementary survey (response rate: 69.8%). Subsequently, 36 participants were omitted from analysis due to scores of 0 on all PBQ items—these participants were not receiving treatment from the Dutch expertise centre for blistering diseases. Sixty-eight participants made up the study population (Table 1). The mean age was 41.1 years (SD ± 16.4), and mean time since diagnosis was 15.3 years (SD ± 8.0). There were 38 (55.9%) males and 30 (44.1%) females. Twenty-nine (42.6%) participants had EBS, ten (14.7%) had JEB, twenty-three (33.8%) had DDEB and six (8.8%) had RDEB [28].

Disease Burden

Self-reported EB-severities were mild (54.4%), moderate (29.4%) and severe (16.2%) (Table 1). Most RDEB participants (66.7%) reported having *severe* EB, followed by JEB (50.0%), DDEB (4.3%) and EBS (3.5%). The majority of participants with DDEB (65.2%) and EBS (51.7%) and all participants with JEB and RDEB had pain. The prevalence of pruritus was high in all EB types (EBS: 58.6%, JEB: 80.0%, DDEB: 82.6% and RDEB: 100%). In the total cohort, a minority of participants were entirely pain-free ($n = 22$, 32.4%) and pruritus-free ($n = 18$, 26.5%).

Treatments

Fewer than half of the participants (47.1%) were using prescribed pharmacologic treatments for pain (Table 2). The most prevalent drug treatment classes for pain were first and second-line analgesics—paracetamol (35.1%) and non-steroidal anti-inflammatory drugs (NSAID) (11.8%). Most DDEB (65.2%) and RDEB (66.7%) patients and half of JEB participants (50.0%) used at least one analgesic drug, whereas not many EBS participants did (27.6%). Only one quarter of all participants reported using pharmacologic pruritus treatments, of which antihistamines (66.7%) were the most prevalent. Of the previously used drug classes for pain and/or pruritus, paracetamol (80.9%), NSAIDs (67.6%), opioids (41.2%) and antihistamines (36.8%) were the most prevalent (Table 2). Twenty-five participants (36.8%) reported having previously not used any of the drug classes listed.

Recreational Drug-Use

Alcohol was the most prevalent recreational drug used (72.1%) and improved symptoms (mostly pain) in seven (14.3%) participants; however, alcohol worsened symptoms (mostly pruritus) in four (8.2%) participants (Table 2). Tobacco-use was less prevalent (17.6%), and no effects on EB-symptoms were reported. Cannabis was used by eight (11.8%) participants, of which five reported symptom reduction. In the total cohort, a minority reported not using any of the listed recreational drugs (20.6%).

Table 1. Demographic and patient-reported characteristics.

	All	EBS	JEB	DDEB	RDEB
Participants, n (%)	68 (100.0)	29 (42.6)	10 (14.7)	23 (33.8)	6 (8.8)
Age, mean ± SD	41.1 ± 16.4	39.7 ± 15.4	49.3 ± 19.4	41.5 ± 16.8	33.2 ± 12.5
Time since diagnosis (years), mean ± SD	15.3 ± 8.0	12.8 ± 7.4	19.6 ± 5.9	16.1 ± 7.9	16.7 ± 11.3
Sex, n (%)					
Female	38 (55.9)	17 (58.6)	4 (40.0)	13 (56.5)	4 (66.7)
Male	30 (44.1)	12 (41.4)	6 (60.0)	10 (43.5)	2 (33.3)
Presence of pain, n (%)	46 (67.6)	15 (51.7)	10 (100)	15 (65.2)	6 (100)

Table 1. Demographic and patient-reported characteristics. (*continued*)

	All	EBS	JEB	DDEB	RDEB
Presence of pruritus, n (%)	50 (73.5)	17 (58.6)	8 (80)	19 (82.6)	6 (100)
Pain NRS, median (IQR)					
Morning	2.0 (0.0–5.0)	0.0 (0.0–2.5) *	6.0 (5.0–7.0) *,**	2.0 (0.0–3.0) **	2.5 (1.0–7.0)
Afternoon	2.0 (0.0–5.0)	0.0 (0.0–2.0) *	5.0 (3.0–7.3) *,**	2.0 (0.0–4.0) **	3.0 (1.0–6.5)
Evening	2.0 (0.0–6.0)	0.0 (0.0–2.5) *	6.0 (5.0–7.3) *,**	2.0 (0.0–6.0) **	4.0 (1.0–7.0)
Mean all-day	2.0 (0.0–5.0)	0.7 (0.0–2.0) *	5.8 (4.8–6.6) *,**	1.3 (0.0–4.3) **	3.2 (1.0–7.1)
Pruritus NRS, median (IQR)					
Morning	1.0 (0.0–3.5)	0.0 (0.0–2.0) *	1.5 (0.0–4.3)	1.0 (0.0–4.0)	4.5 (2.5–7.0) *
Afternoon	1.0 (0.0–3.5)	0.0 (0.0–2.0) *	1.0 (0.0–3.3)	1.0 (1.0–4.0)	3.5 (3.0–5.8) *
Evening	2.0 (0.0–6.0)	1.0 (0.0–4.0)	5.5 (0.8–7.0)	3.0 (1.0–6.0)	5.0 (2.8–7.5)
Mean all-day	1.7 (0.0–4.0)	0.7 (0.0–2.3) *	2.8 (0.5–4.1)	2.0 (1.0–4.6)	4.7 (2.6–6.3) *
Self-reported Severity, n (%)					
Mild	37 (54.4)	19 (65.5)	2 (20.0)	16 (69.6)	0 (0.0)
Moderate	20 (29.4)	9 (31.0)	3 (30.0)	6 (26.1)	2 (33.3)
Severe	11 (16.2)	1 (3.5)	5 (50.0)	1 (4.3)	4 (66.7)

Demographic and participant-reported data describe n = 68 participants within the cohort. Presence of pain and pruritus was determined by mean numeric rating scale values (NRS) >0. (EBS: EB simplex; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB; JEB: junctional EB; SD: standard deviation; IQR: Interquartile range (25th–75th percentage)). (*/**) *represent significant differences (Bonferroni adjusted) between two variables ($p < 0.05$)*

Table 2. (a) Number of current systemic and local pharmacologic treatments for pain and/or pruritus, stratified by EB type.

(a) Treatment Indication	Drug Class	Number of Participants (%)	Number of (Simultaneous) Treatments	Total Count (%) [*n* = 68]	Count by EB-subtype			
					EBS (%) (*n* = 29)	DDEB (%) (*n* = 23)	RDEB (%) (*n* = 6)	JEB (%) (*n* = 10)
Pain	Paracetamol	24 (35.1)	None	36 (52.9)	21 (72.4)	8 (34.8)	2 (33.3)	5 (50.0)
	NSAID	8 (11.8)	1	24 (35.3)	7 (24.1)	11 (47.8)	4 (66.7)	2 (20.0)
	Opioid	3 (4.4)	2	5 (7.4)	1 (3.4)	3 (13.0)	-	1 (10.0)
	Anti-epileptic	2 (2.9)	3	1 (1.5)	-	1 (4.3)	-	-
	CBM	1 (1.5)	4	1 (1.5)	-	-	-	1 (10.0)
			5	1 (1.5)	-	-	-	1 (10.0)
Pruritus	Antihistamine	14 (20.6)	None	51 (75.0)	24 (82.8)	15 (65.2)	4 (66.7)	8 (80.0)
	Calcineurin Inhibitor	3 (4.4)	1	14 (20.6)	5 (17.2)	5 (21.7)	2 (33.3)	2 (20.0)
	Corticosteroid	3 (4.4)	2	2 (2.9)	-	2 (8.7)	-	-
	5HT3-Antagonist	1 (1.5)	3	1 (1.5)	-	1 (4.3)	-	-

Table 2. (b) Number of previous systemic pharmacologic treatments for pain and/or pruritus, stratified by EB type. (*continued*)

(b) Treatment Indication	Drug Class	Number of Participants (%)	Number of Treatments Previously Used	Total Count (%) [*n* = 68]	Count by EB-subtype			
					EBS (%) (*n* = 29)	DDEB (%) (*n* = 23)	RDEB (%) (*n* = 6)	JEB (%) (*n* = 10)
Pain and Pruritus	Paracetamol	55 (80.9)	None	25 (36.8)	11 (37.9)	10 (43.5)	2 (33.3)	2 (20.0)
	NSAID	46 (67.6)	1	6 (8.8)	2 (6.9)	3 (13.0)	-	1 (10.0)
	Opioid	28 (41.2)	2	9 (13.2)	4 (13.8)	3 (13.0)	1 (16.7)	1 (10.0)
	Antihistamine	25 (36.8)	3	11 (16.2)	5 (17.2)	4 (17.4)	1 (16.7)	1 (10.0)
	Steroid	16 (23.5)	4	9 (13.2)	4 (13.8)	1 (4.3)	1 (16.7)	3 (30.0)
	Benzodiazepine	13 (19.1)	5	4 (5.9)	2 (6.9)	-	1 (16.7)	1 (10.0)
	CBM	12 (17.6)	6	1 (1.5)	-	1 (4.3)	-	-
	Antidepressant	10 (14.7)	7	3 (4.4)	1 (3.4)	1 (4.3)	-	1 (10.0)
	Anti-epileptic	4 (5.9)						
	Ketamine	1 (1.5)						

Table 2. (c) Proportion of participantsreporting recreational drug-use and effects on EB. Participants described the effects of any indicated recreational drugsrelated to their "life with EB". More than one could be reported. (*continued*)

(c) Type of Recreational Drug	Number of Participants (%)	Effect on EB, n (%) EB Symptom Reduction	EB Symptom Worsening	Ability to Relax	No effect on EB	Missing
Alcohol	49 (72.1)	7 (14.3)	4 (8.2)	4 (8.2)	6 (12.2)	28 (57.1)
Tobacco	12 (17.6)	-	-	5 (41.7)	3 (25.0)	4 (30.0)
Cannabis	8 (11.8)	5 (62.5)	1 (12.5)	3 (37.5)	1 (12.5)	-
Other drugs	1 (1.5)	-	-	-	1 (100.0)	-
Does not use	14 (20.6)					

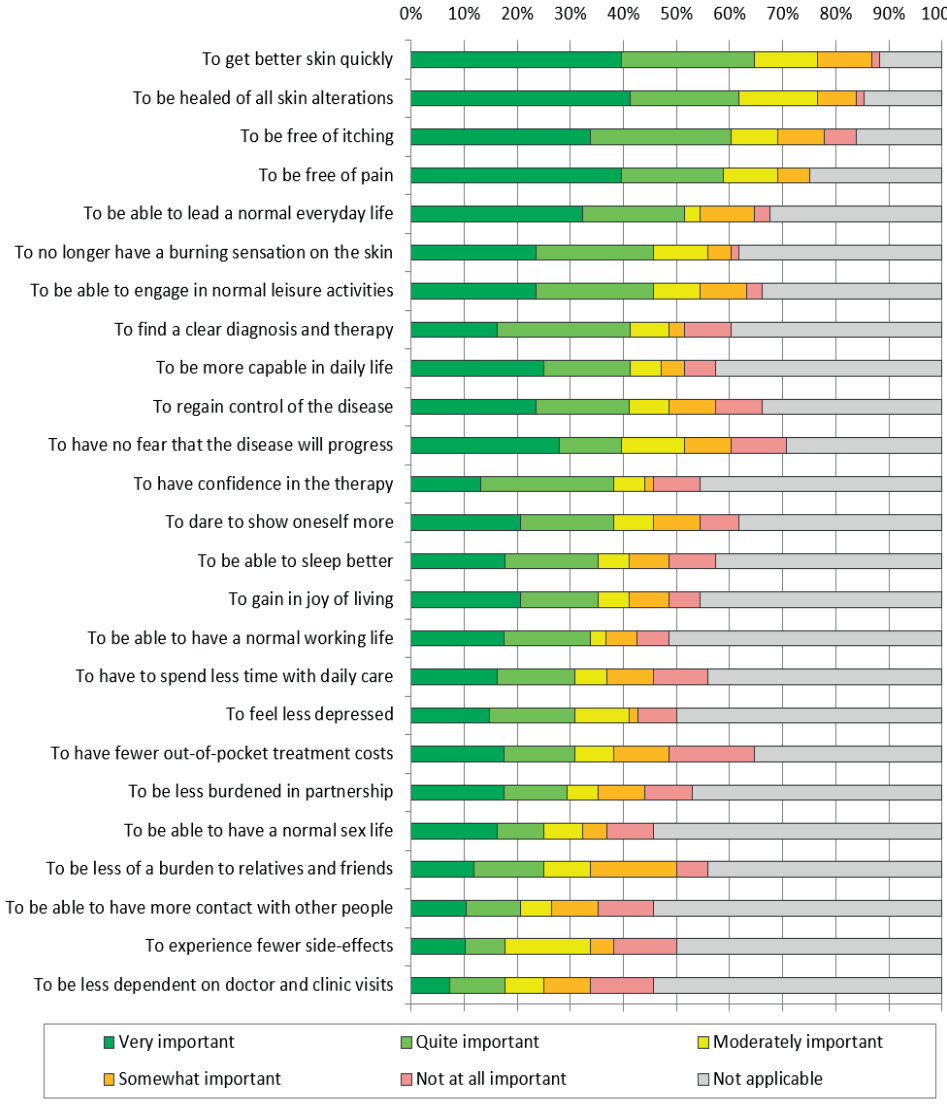


Figure 1. Patient needs questionnaire (PNQ) item importance in all participants in the total cohort (n = 68). Items are ordered by proportions of high importance (very important and quite important).

Patient Benefit Index

The global patient benefit index (PBI) median was 1.34 (IQR: 0.68–2.58, range: 0–4) (Table 3). In 41 participants (60.3%), the global PBI was ≥1, indicating that at least a minimal clinically important difference (MCID) from treatment was achieved. The highest proportion of participants achieving an MCID was observed in JEB (80%), followed by RDEB (66.7%) and DDEB (60.9%). Less than half of EBS participants (48.3%) surpassed this threshold. MCID proportions in male (60%) and female (60.5%) participants were comparable. Significant differences in PBI scores between EB types and sex were not found, nor were any differences observed between the five PBI subscales (Table 3).

Patient Needs

The needs given the highest importance rating (combined percentage of *quite* and *very important*) were *to get better skin quickly* (64.7%) followed by *to be healed of all skin alterations* (61.8%) (Figure 1). The highest importance assigned to needs related to a reduction in symptoms were *to be free of itching* (60.3%), *to be free of pain* (58.8%) and *to no longer have a burning sensation on the skin* (45.6%). Of lowest importance were the needs *to be less dependent on doctor and clinic visits (*17.6%*)* and *to have fewer side effects* (17.6%).

PNQ-items with high importance were stratified by EB type. All RDEB participants gave a high importance rating to the PNQ-items *to be free of itching* (100%) and *to be healed of all skin alterations* (100%). These items were also given the highest importance rating by DDEB participants (*to be healed of all skin alterations* (73.9%), *to be free of itching* (69.6%)). EBS and JEB participants reported the same two needs with highest importance; *to be free of pain* (EBS: 69.0%, JEB: 70.0%) and *to get better skin quickly* (EBS: 58.6%, JEB: 80.0%).

Pairwise comparisons across EB types revealed differences in seven PNQ-items (Figure 2a). RDEB participants assigned a higher importance than EBS to the following items: *to be free of itching* ($Z = -2.80$, 95% Confidence Interval [CI], (0.004–0.006)), *to feel less depressed* ($Z = -2.71$, (0.004–0.007)), *to be less dependent on doctor and clinic visits* ($Z = -2.85$, [0.002–0.004]), *to have to spend less time with daily care* ($Z = -3.92$, (0.000–0.000)) and *to have fewer out of pocket treatment costs* ($Z = -2.91$, (0.001–0.003)). The largest differences between participants with RDEB and DDEB were for the following items: *to have to spend less time with daily care* ($Z = -3.02$, (0.000–0.002)), *to be less of a burden to relatives and friends* ($Z= -2.87$,

(0.002–0.005]) and *to feel less depressed* (*Z* = -2.87, (0.003–0.006)). JEB participants reported a higher importance for the item *to have a normal sex life*, than EBS participants (*Z* = -2.98, (0.002–0.004)).

An exploration of pairwise differences in PNQ-item importance in all participants revealed significant differences between sexes (Figure 2b). Females reported higher importance ratings for *to be free of itching* (*Z* = -2.09, (0.031–0.038)) and *to be able to sleep better* (*Z* = -1.96, (0.040–0.048)).

Table 3. Patient benefit index. Results are presented as median values, interquartile ranges and proportion of participants achieving a score ≥1. (A) PBI is stratified by subtype and sex. (B) PBI subscale scores are represented similarly. *IQR: Interquartile range (25th and 75th percentiles).*

		n	Median (IQR)	Range (min-max)	PBI ≥1 * (%)
(a) PBI	Global	68	1.34 (0.68–2.58)	0.00–4.00	60.3
	EBS	29	0.96 (0.59–2.20)	0.00–3.92	48.3
	RDEB	6	1.35 (0.43–2.34)	0.31–3.52	66.7
	DDEB	23	1.61 (0.80–2.93)	0.00–4.00	60.9
	JEB	10	2.28 (0.84–2.79)	0.32–3.81	80.0
	Male	30	1.41 (0.83–2.86)	0.00–4.00	60.0
	Female	38	1.31 (0.61–2.38)	0.00–4.00	60.5
(b) PBI subscales	Reducing Social Impairments	45	1.43 (0.37–2.67)	0.00–4.00	60.0
	Reducing Psychological Impairments	45	2.00 (0.79–3.00)	0.00–4.00	73.3
	Reducing Impairments due to Therapy	39	1.00 (0.50–3.00)	0.00–4.00	53.8
	Reducing Physical Impairments	63	1.55 (0.63–3.00)	0.00–4.00	71.4
	To have Confidence in Healing	41	1.33 (1.00–3.00)	0.00–4.00	82.9

*A PBI score ≥1 meant that a minimal clinically important difference (MCID) could be assumed.

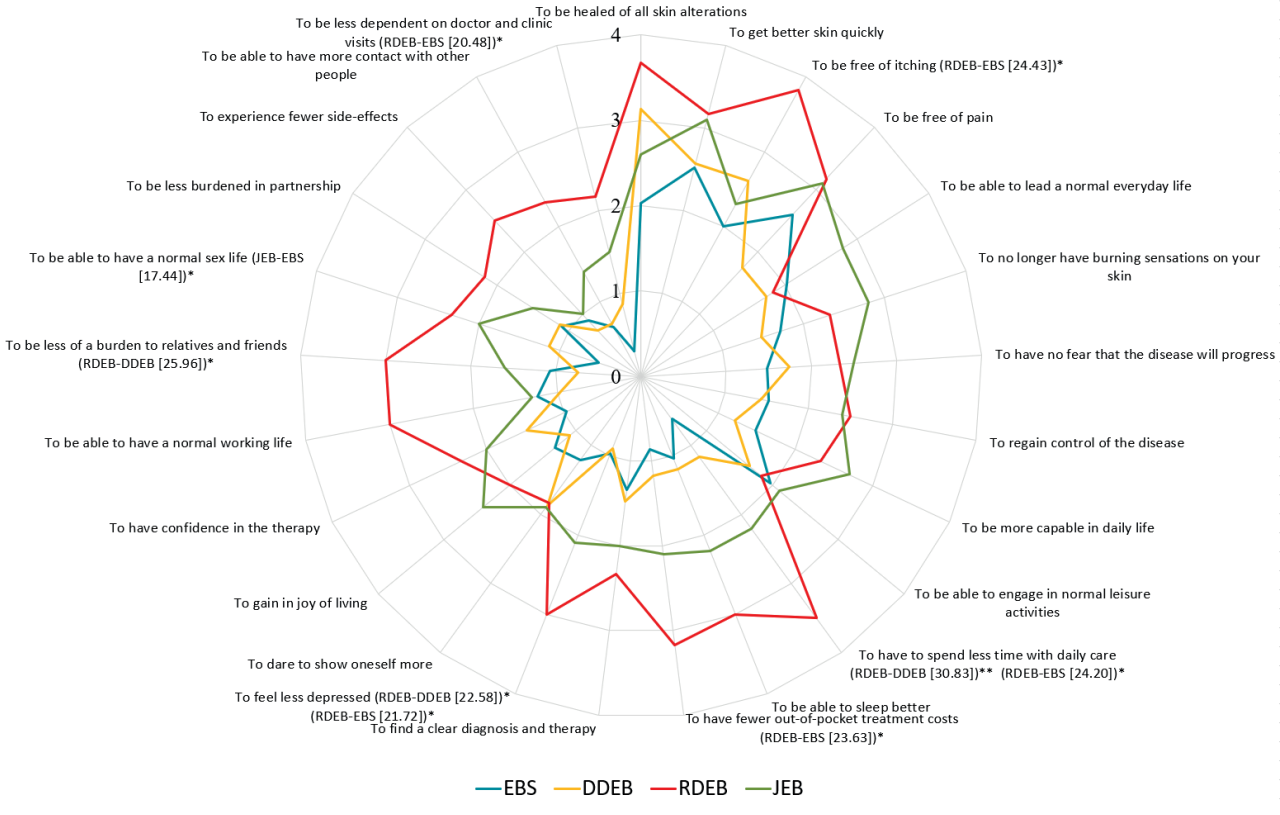


Figure 2. (a) Patient needs questionnaire (PNQ) items representing mean scores in each EB-subtype, in *n* = 68 participants. Chi-square values are shown for items with significant differences between types (EBS, RDEB, DDEB and JEB). Items from A and B are listed in order of high importance in the total cohort. * ($p < 0.05$), ** ($p < 0.01$).

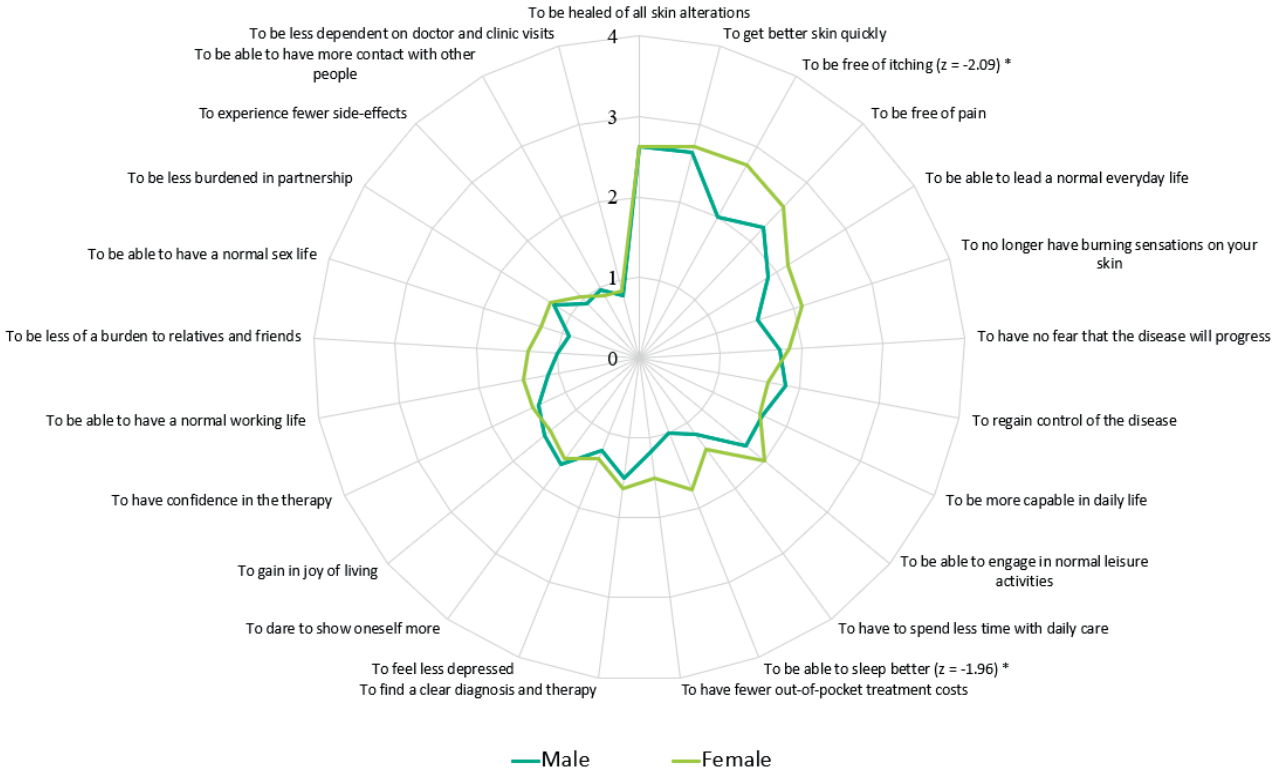


Figure 2. (**b**) PNQ-items representing mean scores in each sex. Z-scores are shown for items with significant differences between sex (male and female). Items from A and B are listed in order of high importance in the total cohort. * ($p < 0.05$), ** ($p < 0.01$). (*continued*)



Figure 3. Scatter diagram in total cohort (n = 68) showing correlation scores of patient-reported outcomes (*pain score; pruritus score; self-reported severity*) and demographic data (*age at time of inclusion; time since diagnosis*) with 25 patient needs questionnaire (PNQ) items. The higher the correlation score, the more positive the correlation. Statistical significance is set to $p < 0.05$ (see figure legend).

Participant-reported disease burden and demographic correlation analysis revealed several positive correlations with PNQ-item importance (Figure 3). Self-reported EB severity moderately correlated with seven PNQ-items, meaning that the more severe participants perceived their EB to be, the more important these needs became. The strongest correlation of self-reported severity was with the item *to feel less depressed* (r_s = 0.636, 95% Confidence Interval [CI] (0.443–0.801)). A moderate correlation was observed between pain scores and the PNQ-item *to gain joy of living* (r_s = 0.510 [0.317–0.660]). For pruritus scores, one moderate correlation was observed (*to be free of itching:* r_s = 0.503 (0.289–0.671)). All correlation scores for age and time since diagnosis were either insignificant or negligible.

DISCUSSION

Burden of Disease

EB comprises a spectrum of disease-severities, of which RDEB and JEB generally make up the most severe EB types [10,16]. In this study, participants with RDEB and JEB reported the highest disease severity, as well as the highest prevalence of pain. By contrast, most EBS and DDEB participants reported a mild severity, and fewer EBS and DDEB participants experienced pain. Pruritus was reported by the majority of participants for each EB type. The highest and lowest prevalence and intensity of pruritus was reported by RDEB and EBS, respectively. Pain and pruritus are by nature complex symptoms of EB, with overlapping aetiologies. Both symptoms can stem from skin or mucosal wounds, inflammation and disrupted epidermal nerve fibres (neuropathies) [6,12,26,51]. Due to ongoing nociceptive and neuropathic pain states, as well as prolonged inflammation in EB, it is likely that nociplasticity occurs [21]. Recalcitrant pain and pruritus are the combined results of pathophysiological processes, the environment and psychosocial factors, which impact the quality of life of EB patients. These symptoms are therefore key determinants of the burden of having EB, because of which the further elucidation of their respective pathoaetiologies deserves the best research-oriented and clinical attention [16,23,45,51,53,56,57].

Therapies

Despite ongoing research, definitive cures have not yet been found for EB [11,31,63]. Enhancing quality of life is therefore important and can be further improved by understanding the needs of patients living with

this disease. It is well known that the most beneficial approach to the symptomatic treatment of EB includes pharmacologic treatment as *one* of the treatment modalities. However, potential benefits are too often overshadowed by limited effectiveness and burdensome side-effects. Concomitant wound/protective dressings, indifferent topical therapy and psychosocial interventions must therefore be used synergistically as the cornerstone of EB treatment [17,26]. Although we observed a high prevalence of pain and pruritus, only three quarters of our participants were currently receiving analgesic or antipruritic pharmacologic therapies. In this cohort, many patients discontinued these treatments. This is likely due to inadequate effects, intolerance to side-effects or the fact that participants only used these treatments for short-term periods. However, based on the collected data, it was not possible to further examine the reasons for discontinuation.

Interestingly, a large discrepancy was seen in the prevalence of previous (n = 28) versus current (n = 3) opioid-use. Whilst opioids are not first-line analgesics in EB, they are modalities for severe acute and chronic pain in EB. Their limited effectiveness and side-effect profiles, including constipation, cognitive impairment, hyperalgesia and pruritus, as well as the risk for tolerance and dependence, may explain the observed discontinuation [5,19].

Recreational Drug-Use

The use of recreational drugs that entail significant health-risks has not yet been assessed in relation to EB. The collection of this data was exploratory and aimed to identify behaviours that may hinder symptom resolution in EB. The minority of participants using tobacco reported no effects on EB symptoms; however, the deleterious effects of tobacco on skin integrity, wound healing and neoplasms are well known [18,49]. Alcohol was the most prevalently consumed drug, because of which a small but noteworthy number of participants reported pain-reduction and pruritus-worsening. This is an important finding as evidence shows that alcohol consumption can induce clinically relevant pain reduction [60]. Therefore its consumption can be motivated by chronic pain and can perhaps demonstrate an inability to find effective analgesia in conventional treatment settings, despite the potential health consequences [67]. For that reason, the persistence of ineffective treatments in EB underpins the need to gain a better understanding of the risks of these behaviours and emphasizes the importance of incorporating appropriate counselling into regular clinical follow-up.

Interestingly, participants in this study reported symptomatic alleviation from cannabis-use. Given the reported benefits of cannabinoid-based medicines (CBMs) in recent studies, it is likely that these participants were self-medicating. The use of cannabinoid-based substances outside the controlled clinical setting outweighed prescribed CBMs in this cohort, which is likely due to the lack of cost reimbursement in the Netherlands. CBMs are gaining traction as potential therapies in EB; two case-series, as well as a recent international survey, highlight a plethora of patient-reported benefits from CBMs [14,44,54,55]. It is therefore imperative that new, high-quality research should ascertain the potential risks and benefits of CBMs in EB care.

Patient Benefit Index (PBI)

The majority of participants achieved the PBI threshold ≥1 for an MCID. Surprisingly, EBS was the only EB type whose MCID proportion was less than half. EBS participants reported the lowest burden of pain and pruritus, highest proportion of mild EB and lowest importance ratings for the PNQ-items. Although EBS is often considered mild, this may not mean that their needs are more readily met. In fact, milder clinical presentations and subjective disease experiences imply that the window of opportunity for meaningful outcome improvements in EBS is smaller. By contrast, a recent study highlighted unmet pain treatment needs in EBS that significantly impacted overall QoL [12]. These unmet treatment needs and benefits in EBS patients warrant further investigation to ascertain the observed pitfalls in recognizing and fulfilling EBS care needs. Utilizing the PBI-S may add value to clinical decisions based on patient-relevant needs.

Patient Needs: Items

The most important needs identified in this study were within the physical manifestations of EB (*to get better skin quickly* and *to be healed of all skin alterations*). Promising therapeutic research continually addresses underlying genetic defects, skin integrity, fibrosis and neoplasms; however, the findings in this study may reflect high patient expectations that, to date, are still unattainable in EB patient care [15,27,31,48]. It is critical that clinicians address the discrepancy between feasible treatment goals and patient expectations in EB, through adequate, repeated patient counselling, as existing evidence for other conditions show that expectation management improves perceived outcomes [25,37,40].

The significant burden of symptoms in EB is well known, and this was reflected in our study as symptomatic needs in all EB types were ranked highly (*to be free of pain, to be free of itching* and *to no longer have a burning sensation on the skin*). Unlike the physical manifestations of EB, symptoms such as pain and pruritus tend to be more tangible therapeutic targets. However, even with numerous treatment modalities, adequate symptomatic alleviation is a challenging feat. As a result, patients often develop coping strategies in a desperate attempt to manage these symptoms [41].

RDEB participants reported the highest frequency and importance for all needs. RDEB is characterized as a severe EB-type, with a high symptomatic burden and excessive home-based and clinical care needs [1,33,50]. In this study, this was reflected in the higher frequency and importance assigned to the following needs by RDEB participants: *to have to spend less time with daily care, to be less of a burden to relatives/friends, to have fewer out of pocket treatment costs* and *to be less dependent on clinical visits*. These same PNQ-items were less important for all other EB-types, thus distinguishing RDEB-needs; minimizing the care-related burden in RDEB remains a priority.

Previous studies have shown differences in depressive symptoms between DEB (RDEB and DDEB together) and control groups [22,23]. However, in this study the item *to feel less depressed* was significantly more important for RDEB than for DDEB participants. Depressive symptoms in RDEB should be given adequate clinical attention, as these may worsen the perceived pain, and vice versa [36]. Furthermore, subdividing DEB into DDEB and RDEB when assessing depressive symptoms in research settings is imperative.

The PNQ analysis also highlighted more obscure patient needs, such as *to be able to have a normal sex-life*, which was significantly more important in JEB compared to EBS. Sexuality in relation to EB is underrepresented in the scientific literature; however, new international EB consensus guidelines on sexuality have been published [35,43].

Two PNQ-items, *to be free of itching* and *to be able to sleep better,* were significantly more important for females than males. Similar differences in the burden of pruritus between sexes in EB has been observed [59,66]. In other pruritic diseases, females report higher intensity scores and impact on QoL than men, which is likely exacerbated by emotional and psychosomatic factors [58]. Therefore, sex differences and emotional burdens in

EB, especially in females, should be considered during pruritus oriented EB consultations. The negative effects of pruritus on quality of sleep are well described in other conditions, which may explain why females, with a higher need to reduce itching, also assigned a higher importance to the need related to sleep [39].

Patient Needs: Correlations

The correlation analysis revealed that a higher self-reported EB severity, irrespective of EB type, correlated with higher importance of needs in all but two PNQ-items. Patients' perception of the severity of their EB is shaped by physical, sociodemographic, psychological factors, coping mechanisms and expectations [32]. Utilizing self-reported severity measurements awards clinicians with additional insight into the perceived disease burden, and subsequent individualised needs assessments further provide a backbone to formulating treatment goals. The needs *to dare to show oneself more* and *to be able to lead a normal everyday life* did not correlate with self-reported severity. This indicates that psychosocial support related to self-image and well-being is equally necessary for any EB severity, and is in line with recent EB guidelines on psychosocial support [43]. Using a structured survey such as the PBI can enhance clinical care attuned to psychosocial needs.

Pain scores correlated well with the majority of PNQ-items, which suggests the far reaching consequences of pain on daily life in EB [26,66]. By contrast, pruritus scores only correlated with two needs: *to be free of itching* and *to be able to sleep better.* Sparse research has assessed sleep quality in EB; however, one study observed disturbed sleeping patterns in DEB patients [24]. Other studies report that any EB type is at risk of negatively affected sleep quality [16,57,64]. These findings indicate a bi-directional interplay of sleep quality and symptoms, whereby improving either factor will positively affect the other. Even though the prevalence of pruritus in this cohort was high, the use of sedative antihistamine and anxiolytic medications, conventionally used to improve pruritus and aid sleep, was low, which may be due to their minimal effectiveness for pruritus in EB.

The absence of correlations between age and PNQ-items is an important finding, indicating that age does not influence adult EB-patient needs. As patients get older, it is unclear if their ability to deal with the physical and psychosocial consequences of EB improves. One study, however, observed correlations between stress and age, suggest that, as time goes

by, patients adapt to the complications of their EB [46]. Additionally, in non-EB chronic pain, the relationship between pain and disability is more pronounced in younger people, and meta-analyses demonstrate dynamic age-related pain tolerance [30,38,52]. Although an age-to-needs relationship was not observed in this study, future research assessing the natural history of symptoms in EB could add important value to current paradigms in EB care.

Strenghts and Limitations

To the best of our knowledge, this is the first study of EB to implement a survey that assesses patient benefit outcomes weighted by individual needs. The results in this study complement existing qualitative and cross-sectional research on patient needs and consequences of living with EB [10,33,34,57]. The response rate in this study was high compared to other cross-sectional EB studies in our centre and demonstrates participants' willingness to be involved in research that addresses their individual needs [56,57,66].

The PBI-S is designed to be implemented before and after an intervention. In our explorative design we omitted the assessment of a specific treatment in favour of "general EB clinical care at the UMCG". This resulted in PBI scores not representing benefits from any single intervention. Additionally, participants were not pre-conditioned to score their needs based on "ideal" versus "realistic" expectations from EB care interventions, which means that some may have accounted for this when others did not. This may partially explain the low proportions of MCID achieved by participants. However, the limited effectiveness of conventional treatments still appears to be an important factor leading to inadequate treatment effectiveness and persistence of unmet needs in EB.

Importantly, we were unable to mitigate certain biases due to the retrospective nature of benefit reporting in the PBQ and pain/pruritus NRS. A recall bias may have been present when patients reported benefits, previous treatments and symptom scores. As recreational drug-use is a sensitive topic, patients were encouraged to be transparent when reporting; however, underreporting should be considered. Additionally the present state effect bias (how a participant feels at the moment of survey completion) is likely to have influenced the survey results; therefore, participants may have over- or under-reported their treatment benefits [7].

Although the PBI-S has been validated for general dermatologic conditions, we expect that it overlooks treatment goals unique to EB. Additionally, the PBI is limited in its assessment of benefits, insofar that it cannot assess worsening of symptoms or distancing from treatment goals due to therapy. Future studies should validate EB-specific PBI items through a combined patient and clinician consensus [2,20,42,68].

CONCLUSIONS

Effective treatments for EB remain elusive, and patient needs are not readily met. This study highlights an important discrepancy between patient needs and the feasible capabilities of the available treatments. The role of patient expectation management through transparent, informed and compassionate communication should be emphasized by healthcare-providers in the clinical setting in order to improve perceived treatment outcomes in EB. Utilizing outcome tools such as the PBI-S in conjunction with well-established multidisciplinary care may catalyze the process of tailoring treatments to the needs of individuals with EB. Furthermore, these results emphasize the continued need for developing effective treatments for EB and its accompanying symptoms in order to improve patients' quality of life.

ACKNOWLEDGMENTS

Our utmost appreciation goes to the participants with EB who kindly gave their time for this study, Laura Loman MD, and Hildegard Franke for assistance in data collection, and Rosalie Baardman MD, for overseeing database extractions. We would also like to acknowledge both DEBRA-NL and DEBRA-UK for their continued involvement in, and funding of patient centred research. Finally, to acknowledge H Schräder MD, who for this study inspired the authors to look beyond conventional needs assessments in EB.

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Table A: Patient-rated importance of needs in all EB types from the Patient Needs Questionnaire (PNQ) (n=68). B) Patient-rated importance (percentage) of needs using the PNQ, stratified by EB type

A						B			
PBI Subscale	**Patient Needs Questionairre (PNQ) item**	**mean (SD)**	**median (IQR)**	**Does apply: n (%)**	**Proportion of high importance: n (%)**	**Percentage (%) proportion of high importance by EB type**			
						EBS (n=29)	*DDEB (n=23)*	*RDEB (n=6)*	*JEB (n=10)*
Having Confidence in Healing	To find a clear diagnosis and therapy	1.57 (1.65)	1 (0-3)	41 (60.3)	28 (41.2%)	41.4	30.4	66.7	50.0
	To have no fear that the disease will progress	1.79 (1.71)	2 (0-4)	48 (70.6)	27 (39.7%)	31.0	30.4	66.7	70.0
	To have confidence in the therapy	1.41 (1.63)	0 (0-3)	37 (54.4)	26 (38.2%)	27.6	39.1	66.7	50.0
Reducing Impairments due to Therapy	To have to spend less time with daily care	1.29 (1.61)	0 (0-3)	38 (55.9)	21 (30.9%)	13.8	30.4	83.3	50.0
	To have fewer out-of-pocket treatment costs	1.35 (1.62)	0 (0-3)	44 (64.7)	21 (30.9%)	17.2	26.1	83.3	50.0
	To experience fewer side-effects	1.00 (1.42)	0 (0-2)	34 (50.0)	12 (17.6%)	17.2	8.7	66.7	10.0
	To be less dependent on doctor and clinic visits	0.84 (1.35)	0 (0-1.5)	31 (45.6)	12 (17.6%)	6.9	17.4	50.0	30.0

Table A: Patient-rated importance of needs in all EB types from the Patient Needs Questionnaire (PNQ) (n=68). B) Patient-rated importance (percentage) of needs using the PNQ, stratified by EB type (*continued*)

A						B			
PBI Subscale	**Patient Needs Questionairre (PNQ) item**	**mean (SD)**	**median (IQR)**	**Does apply: n (%)**	**Proportion of high importance: n (%)**	**Percentage (%) proportion of high importance by EB type**			
Reducing Physical Impairments	To be healed of all skin alterations	2.63 (1.49)	3 (2-4)	58 (85.3)	42 (61.8%)	41.4	73.9	100.0	70.0
	To be free of itching	2.41 (1.57)	3 (1-4)	57 (83.8)	41 (60.3%)	48.3	69.6	100.0	50.0
	To be free of pain	2.43 (1.64)	3 (0.5-4)	51 (75.0)	40 (58.8%)	69.0	34.8	83.3	70.0
	To no longer have a burning sensation on the skin	1.85 (1.68)	2 (0-4)	42 (61.8)	31 (45.6%)	44.8	34.8	66.7	60.0
	To be able to sleep better	1.43 (1.65)	0 (0-3)	39 (57.8)	24 (35.3%)	24.1	26.1	83.3	60.0
Reducing Psychological Impairments	To be able to lead a normal everyday life	2.03 (1.74)	3 (0-4)	46 (67.6)	35 (51.5%)	48.3	47.8	50.0	70.0
	To be able to engage in normal leisure activities	1.87 (1.66)	2 (0-3)	45 (66.2)	31 (45.6%)	48.3	39.1	50.0	50.0
	To gain in joy of living	1.46 (1.69)	0 (0-3)	37 (54.4)	24 (35.3%)	31.0	30.4	33.3	60.0
	To feel less depressed	1.29 (1.61)	0 (0-3)	34 (50.0)	21 (30.9%)	24.1	21.7	83.3	40.0

Table A: Patient-rated importance of needs in all EB types from the Patient Needs Questionnaire (PNQ) (n=68). B) Patient-rated importance (percentage) of needs using the PNQ, stratified by EB type (*continued*)

A						B			
PBI Subscale	**Patient Needs Questionairre (PNQ) item**	**mean (SD)**	**median (IQR)**	**Does apply: n (%)**	**Proportion of high importance: n (%)**	**Percentage (%) proportion of high importance by EB type**			
	To be more capable in daily life	1.65 (1.75)	1 (0-3.5)	39 (57.4)	28 (41.2%)	34.5	30.4	66.7	70.0
Reducing Social Impairments	To dare to show oneself more	1.59 (1.67)	1 (0-3)	42 (61.8)	26 (38.2%)	27.6	43.5	50.0	50.0
	To be able to have a normal working life	1.31 (1.67)	0 (0-3)	33 (48.5)	23 (33.8%)	31.0	26.1	83.3	30.0
	To be less burdened in partnership	1.26 (1.63)	0 (0-3)	36 (52.9)	20 (29.4%)	27.6	26.1	50.0	30.0
	To be able to have a normal sex life	1.10 (1.59)	0 (0-2.5)	31 (45.6)	17 (25.0%)	10.3	26.1	66.7	40.0
	To be less of a burden to relatives and friends	1.21 (1.47)	0.5 (0-2.5)	38 (55.9)	17 (25.0%)	17.2	17.4	83.3	30.0
	To be able to have more contact with other people	0.93 (1.44)	0 (0-2)	31 (45.6)	14 (20.6%)	10.3	17.4	66.7	30.0
Unspecified	To get better skin quickly	2.68 (1.43)	3 (2-4)	60 (88.2)	44 (64.7%)	58.6	60.9	83.3	80.0
	To regain control of the disease	1.71 (1.69)	1 (0-3)	45 (66.2)	28 (41.2%)	34.5	34.8	66.7	60.0

Table B: Correlation scores of patient-reported outcomes (pain score; pruritus score; self-reported severity) and demographic data (age at time of inclusion; time since diagnosis) with 25 patient needs questionnaire (PNQ) items

	Age at time of inclusion Coefficient [Confidence interval]		Time since diagnosis Coefficient [Confidence interval]		Self-reported severity Coefficient [Confidence interval]		Pain score Coefficient [Confidence interval]		Pruritus score Coefficient [Confidence interval]	
To get better skin quickly	-0.017	[-0.258 - 0.250]	-0.167	[-0.410 - 0.097]	*0.325	[0.108 - 0.508]	*0.385	[0.147 - 0.608]	-0.001	[-0.249 - 0.243]
To be healed of all skin alterations	0.104	[-0.177 - 0.354]	-0.086	[-0.307 - 0.142]	*0.325	[0.093 - 0.531]	*0.363	[0.095 - 0.578]	0.057	[-0.201 - 0.301]
To be free of itching	0.100	[-0.142 - 0.354]	0.184	[-0.067 - 0.416]	*0.335	[0.116 - 0.538]	0.232	[-0.021 - 0.471]	*0.503	[0.289 - 0.671]
To be free of pain	-0.095	[-0.332 - 0.143]	-0.041	[-0.285 - 0.215]	*0.381	[0.178 - 0.545]	*0.367	[0.151 - 0.574]	0.045	[-0.185 - 0.280]
To be able to lead a normal everyday life	-0.053	[-0.319 - 0.203]	0.030	[-0.225 - 0.281]	*0.283	[0.038 - 0.482]	*0.434	[0.210 - 0.625]	0.044	[-0.170 - 0.292]
To no longer have a burning sensation on the skin	0.205	[-0.058 - 0.430]	-0.079	[-0.349 - 0.194]	*0.432	[0.197 - 0.624]	*0.498	[0.284 - 0.664]	0.098	[-0.142 - 0.357]
To be able to engage in normal leisure activities	-0.011	[-0.233 - 0.211]	-0.006	[-0.278 - 0.258]	*0.391	[0.177 - 0.564]	*0.427	[0.175 - 0.614]	-0.036	[-0.266 - 0.194]
To find a clear diagnosis and therapy	0.200	[-0.061 - 0.440]	0.096	[-0.163 - 0.367]	*0.382	[0.154 - 0.567]	*0.398	[0.163 - 0.598]	-0.086	[-0.319 - 0.160]
To be more capable in daily life	-0.101	[-0.374 - 0.174]	0.071	[-0.178 - 0.336]	*0.513	[0.298 - 0.672]	*0.415	[0.160 - 0.627]	0.036	[-0.199 - 0.302]
To regain control of the disease	0.026	[-0.228 - 0.271]	-0.137	[-0.361 - 0.105]	*0.428	[0.182 - 0.622]	*0.356	[0.089 - 0.591]	0.056	[-0.186 - 0.285]

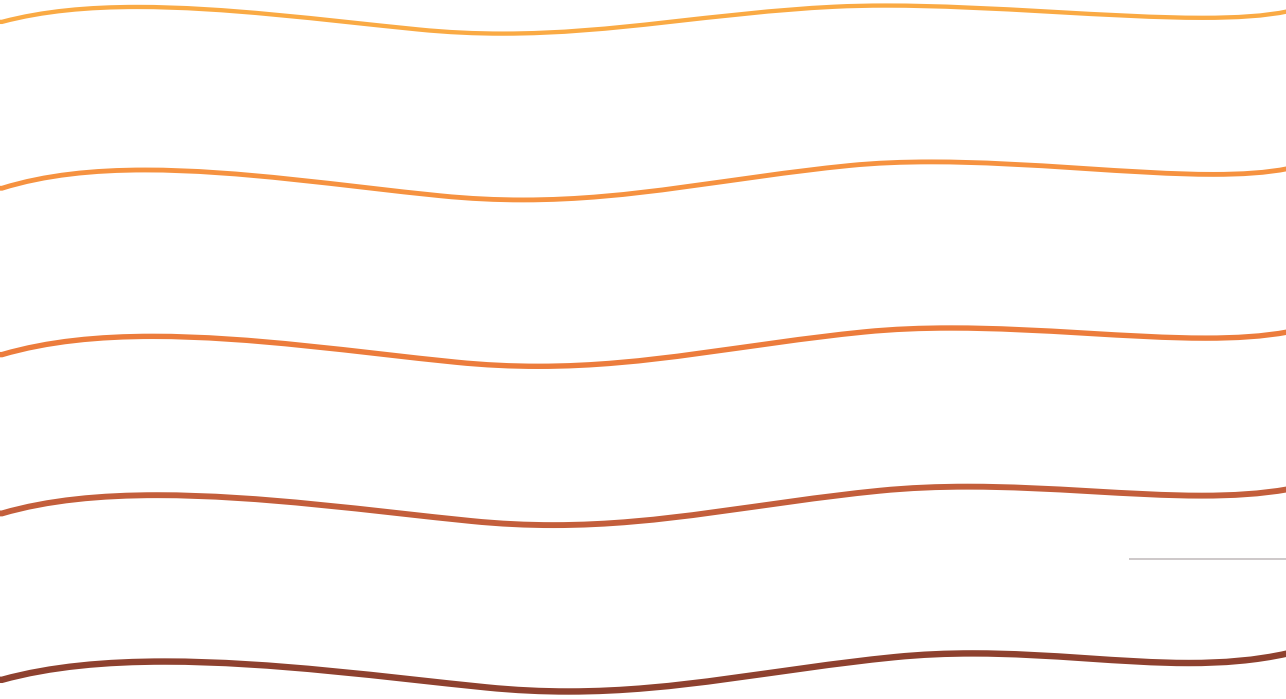
Table B: Correlation scores of patient-reported outcomes (pain score; pruritus score; self-reported severity) and demographic data (age at time of inclusion; time since diagnosis) with 25 patient needs questionnaire (PNQ) items (*continued*)

	Age at time of inclusion Coefficient [Confidence interval]		Time since diagnosis Coefficient [Confidence interval]		Self-reported severity Coefficient [Confidence interval]		Pain score Coefficient [Confidence interval]		Pruritus score Coefficient [Confidence interval]	
To have no fear that the disease will progress	*0.267	[0.045 – 0.451]	-0.024	[-0.285 – 0.249]	*0.327	[0.077 – 0.542]	*0.320	[0.076 – 0.555]	0.017	[-0.240 – 0.275]
To have confidence in the therapy	0.195	[-0.670 – 0.440]	0.089	[-0.171 – 0.375]	*0.439	[0.196 – 0.641]	*0.443	[0.238 – 0.611]	-0.027	[-0.267 – 0.212]
To dare to show oneself more	0.094	[-0.162 – 0.329]	0.002	[-0.239 – 0.227]	0.210	[-0.042 – 0.443]	*0.304	[0.066 – 0.514]	0.054	[-0.177 – 0.295]
To be able to sleep better	0.088	[-0.147 – 0.302]	0.134	[-0.108 – 0.337]	*0.550	[0.343 – 0.731]	*0.494	[0.288 – 0.665]	*0.397	[0.180 – 0.590]
To gain joy of living	0.106	[-0.145 – 0.341]	0.063	[-0.190 – 0.324]	*0.488	[0.262 – 0.678]	*0.510	[0.317 – 0.660]	0.009	[-0.235 – 0.212]
To be able to have a normal working life	-0.065	[-0.298 – 0.169]	0.034	[-0.247 – 0.321]	*0.418	[0.107 – 0.179]	*0.331	[0.099 – 0.536]	-0.022	[-0.270 – 0.226]
To have to spend less time with daily care	0.131	[-0.103 – 0.342]	0.222	[-0.052 – 0.460]	*0.544	[0.339 – 0.718]	*0.426	[0.207 – 0.619]	0.109	[-0.146 – 0.335]
To feel less depressed	0.035	[-0.206 – 0.285]	0.115	[-0.159 – 0.362]	*0.636	[0.443 – 0.801]	*0.431	[0.209 – 0.619]	0.017	[-0.254 – 0.255]
To have fewer out of pocket treatment costs	0.021	[-0.235 – 0.264]	0.226	[-0.013 – 0.450]	*0.539	[0.330 – 0.694]	*0.373	[0.146 – 0.561]	0.161	[-0.089 – 0.414]
To be less burdened in partnership	-0.011	[-0.255 – 0.229]	0.024	[-0.241 – 0.285]	*0.333	[0.111 – 0.523]	*0.310	[0.099 – 0.504]	0.101	[-0.143 – 0.326]

Table B: Correlation scores of patient-reported outcomes (pain score; pruritus score; self-reported severity) and demographic data (age at time of inclusion; time since diagnosis) with 25 patient needs questionnaire (PNQ) items (*continued*)

	Age at time of inclusion Coefficient [Confidence interval]		Time since diagnosis Coefficient [Confidence interval]		Self-reported severity Coefficient [Confidence interval]		Pain score Coefficient [Confidence interval]		Pruritus score Coefficient [Confidence interval]	
To be able to have a normal sex life	0.123	[-0.102 - 0.354]	0.241	[-0.022 - 0.488]	*0.476	[0.239 - 0.671]	*0.354	[0.120 - 0.553]	*0.231	[0.017 - 0.437]
To be less of a burden to relatives and friends	-0.135	[-0.388 - 0.111]	0.177	[-0.091 - 0.418]	*0.556	[0.357 - 0.728]	*0.327	[0.066 - 0.552]	-0.024	[-0.258 - 0.208]
To be able to have more contact with other people	0.084	[-0.184 - 0.329]	0.228	[-0.002 - 0.124]	*0.493	[0.223 - 0.704]	*0.266	[0.021 - 0.493]	-0.093	[-0.324 - 0.110]
To experience fewer side-effects	0.175	[-0.059 - 0.419]	*0.286	[0.028 - 0.504]	*0.332	[0.086 - 0.541]	*0.267	[0.015 - 0.477]	0.094	[-0.147 - 0.318]
To be less dependent on doctor and clinic visits	0.117	[-0.113 - 0.351]	*0.282	[0.027 - 0.510]	*0.525	[0.289 - 0.706]	*0.413	[0.209 - 0.599]	0.184	[-0.054 - 0.405]

*Correlation is significant at the 0.05 level (2-tailed).
Degrees of correlation: 0.000-0.299 (negligible), 0.300-0.499 (low), 0.500-0.699 (moderate), 0.700-1.00 (high)



Chapter

3

The Pain Quality Assessment Scale for Epidermolysis Bullosa

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Acta Derm Venereol. 2018 Mar 13;98(3):346–349

ABSTRACT

Pain is one of the most debilitating symptoms in epidermolysis bullosa (EB) leading to a reduced quality of life. Pain in EB is comprises both neuropathic and non-neuropathic qualities. An assessment of pain qualities has not formerly been completed in EB. The Pain Quality Assessment Scale (PQAS) is an adjusted version of the validated Neuropathic Pain Scale and includes 20 pain qualities and descriptors.

Patients with EB (n = 43) answered 20 numerical scale and one multiple choice question in the PQAS pertaining to pain qualities. Pain was experienced by 39 patients (91%). In general patients with EB suffer from intense and unpleasant pain located on the surface of the skin; the hands and feet are most commonly affected. The subtypes, recessive dystrophic EB and junctional EB reported pain qualities pathognomonic of neuropathic pain. The PQAS provides additional value to current practice of global pain intensity scoring in EB.

INTRODUCTION

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of inherited mucocutaneous blistering disorders that lead to painful erosions, strictures and contractures. The incidence of EB is 1:22,000 births and the prevalence is 2.4:100,000 [1]; a total of 587 patients are currently registered in the Netherlands (population approximately 17 million). The disease is caused by mutations in structural proteins maintaining the integrity of stratified squamous epithelia. The splitting of skin and mucous membranes and subsequent blistering lead to a cascade of secondary effects that require comprehensive multidisciplinary clinical care, in which pain has been identified as one of the most significant and unbearable aspects[3].

Pain in epidermolysis bullosa

The most important issues in EB include the symptoms experienced by patients on a daily basis. One of the greatest challenges reported by patients is controlling pain during dressing changes [6]. Therefore, new research on effective pain alleviation, improving best-practice guidelines, will have an immediate and far-reaching effect on clinical practice.

EB research encompassing pain has been limited by a tendency to highlight global pain intensity rather than measure individual qualities of pain [10]. This is in contrast to current consensus that pain qualities or descriptors can aid the clinical classification of the nature of pain (e.g. neuropathic) and give direction to appropriate treatments [4]. Not identifying the qualities of pain limits the ability to tailor treatment regimens for individual patients, as pharmacological treatments of neuropathic and non-neuropathic pain differ, and exposes patients to unnecessary health risks and healthcare costs for analgesic medicines [8].

Pain in EB is highly associated with wound presentation, is extremely debilitating, and correlates strongly with a reduction in patients' quality of life (QoL) [6].

The general consensus is that pain in EB is caused by neuropathic and non-neuropathic mechanisms, probably exacerbated by central nervous system sensitization and psychological conditioning. Pain associated with extensive wounds show neuropathic qualities as it has a "burning" sensation. A recent study confirmed a source of neuropathic pain as they showed a decreased intraepidermal nerve fibre density in patients with

RDEB, caused by injury (probably due to trauma, metabolic-toxins, infections and nutritional deficits, amongst others) to the distal terminals of small fibres [2].

The most updated set of evidence-based best-practice EB guidelines addresses the many painful scenarios or events, including pain from surgery, chronic wounds, dressing changes, baths, ulcerative lesions, gastrointestinal tract, bones, corneal abrasions and end-of-life scenarios [6]. In the daily life of patients with EB, analgesia is key to coping with painful symptoms of multisystem disease. The use of allopathic drugs for every cause of pain may lead to a level of sedation that will hinder normal productivity and the ability to perform other daily activities. This poses a problem, as there is not one form of adequate pain therapy for these patients.

The complex pathophysiology of EB means that the causes of pain cannot always be identified and treated appropriately. The aim of this study is to harness the clinical descriptors of pain qualities in EB by applying the Pain Quality Assessment Scale (PQAS), which will enable more accurate assessment of treatment and intervention outcomes through patient-reported pain qualities.

MATERIAL AND METHODS

Design

This study is a cross-sectional survey for patients diagnosed with any subtype of EB, registered at the Center for Blistering Diseases at the Department of Dermatology, University Medical Center Groningen (UMCG).

Survey: Pain Quality Assessment Scale

The translated Dutch PQAS questionnaire describes the levels and qualities of pain experienced by participants in the last week.[9] The PQAS is an adapted version of the clinically validated Neuropathic Pain Scale (NPS), [5] containing 10 additional pain descriptors. We selected the PQAS for this study because of its broad inclusion of neuropathic and non-neuropathic pain qualities. All participants completed the PQAS once and were asked to rate the severity of each of the 20 pain qualities using a numerical rating scale (0 = no pain/sensation; 10 = the most pain/sensation imaginable) and 1 multiple-choice question on the temporal quality of pain (Table 1).

Table 1: Definitions of time qualities of pain as described to patients completing the PQAS survey

	Definition referred to in the PQAS
Intermittent	I feel pain sometimes but I am pain-free at other times
Variable	"background" pain all the time, but also moments of more pain, or even severe "breakthrough" pain or varying types of pain
Stable	constant pain that does not change very much from one moment to another, and no pain-free periods

Data analysis

Means and standard deviations were calculated for all pain qualities. The diagnosis EB was divided into 4 genetic subtypes, EB simplex (EBS), junctional EB (JEB), RDEB, and dominant dystrophic EB (DDEB). Statistical differences were calculated using independent samples t-testing with a significance of $p < 0.05$ on IBM's SPSS software.

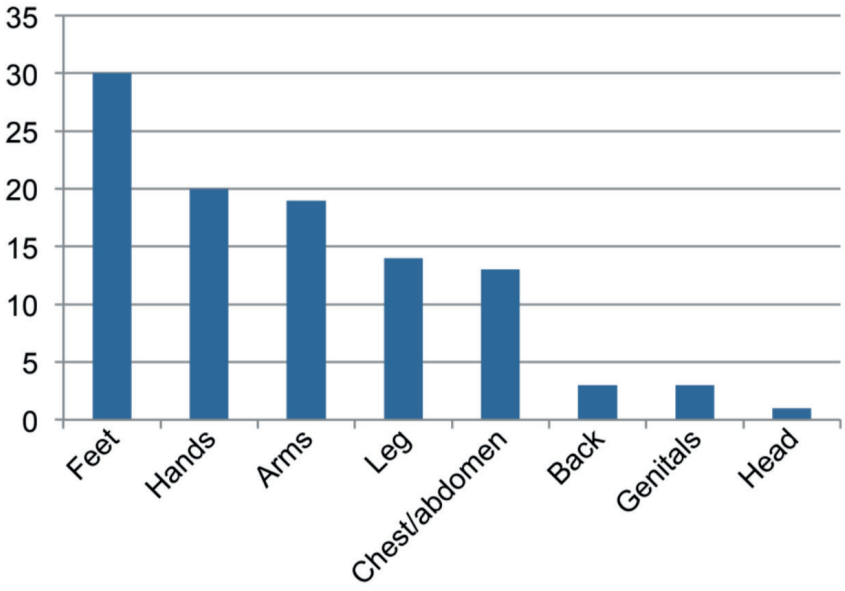


Figure 1: Frequency of Anatomical Locations of Pain in Epidermolysis Bullosa (n = 35). Multiple locations may be recorded on one patient

Ethical consideration

Ethical approval to complete this study was obtained from the ethics board of the UMCG.

RESULTS

Patients

The PQAS was sent to 134 patients and was completed by 43 patients (response rate 32%). Thirty-nine patients (91%) experienced pain by scoring higher than zero for at least 1 parameter of pain (RDEB = 5; DDEB = 9; EBS = 19; JEB = 6).

Pain Quality Assessment Scale

The general trend in the entire study portrayed patients with EB as experiencing *intense* and *unpleasant* pain located on the *surface* of the skin (Figure 2). The feet and hands were the most commonly affected anatomical locations, followed by arms and legs, provided in Figure 1. The global measurement of pain (*intense)* showed that JEB and RDEB scored the highest with means of 5.5 and 5.4, out of 10, respectively, significantly higher than EBS patients who scored a mean of 2.4. The *unpleasant* experience of pain (described by the words *annoying, bothersome, miserable* and *intolerable* was given the highest score of the 20 qualities, in 3 of the 4 subtypes (RDEB = 6.4; EBS = 3.5; JEB = 5.7). DDEB attributed the highest score to pain with an *itchy* sensation (5.7). High mean scores for a *sharp* pain was reported by RDEB (5.8) and JEB (5.3), whereas EBS attributed higher mean scores to *sensitive* (2.7) and *tender* (2.8) pain qualities.

The results show a trend that patients with JEB, DDEB and RDEB scored higher means than those with EBS on 18 of 20 parameters (Table 2). As well as experiencing significantly more *intense* pain, patients with RDEB and DDEB reported significantly higher means for *itchy* pain compared with those with EBS. Patients with RDEB also scored significantly higher means for *sharp, shooting, unpleasant* and *surface* pain compared with those with EBS.

A *cold* -type pain sensation was experienced least by all respondents and was reported as the lowest score in patients with RDEB (2.0), DDEB (0.1) and EBS (0.5). Patients with JEB scored similarly low (1.8), however reported a *cramping* type pain with the lowest score (1.2).

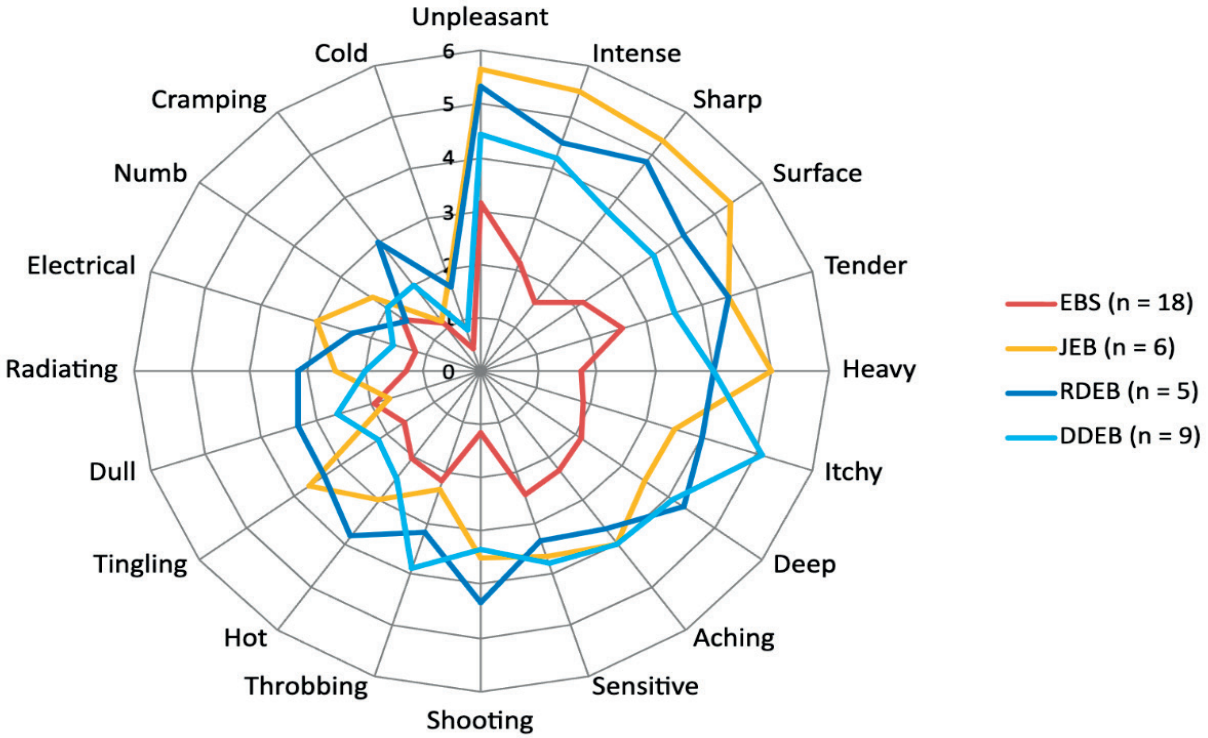


Figure 2: Radar diagram portraying mean scores (0 to 10) of pain qualities from the PQAS for each epidermolysis bullosa subtype. EBS: EB simplex; JEB: junctional EB; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB.

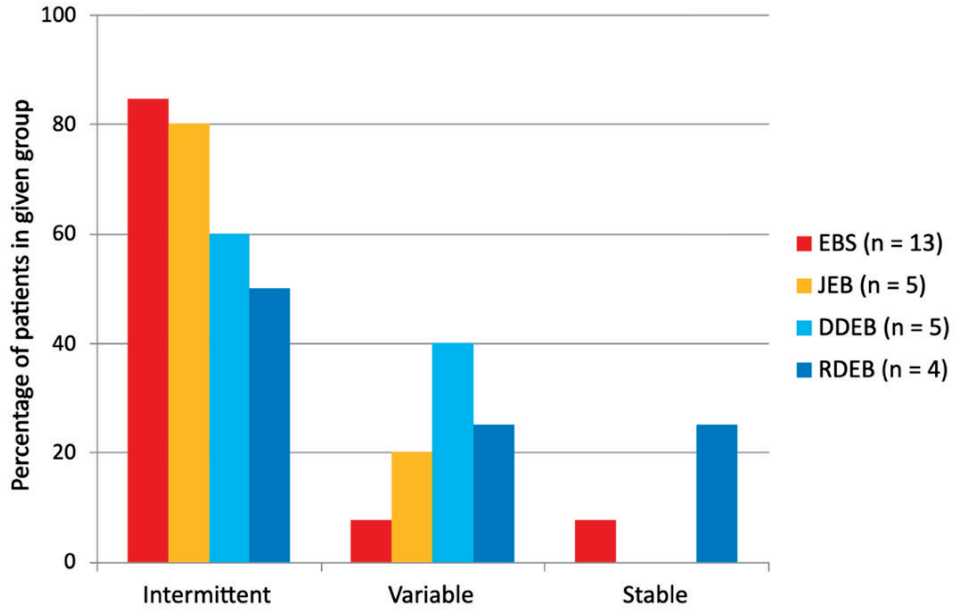


Figure 3: Time quality of pain per epidermolysis bullosa subtype of respondents, shown in percentages. I) Intermittent: I feel pain sometimes but I am pain-free at other times. II) Variable: "Background" pain all the time, but also moments of more pain, or even severe "breakthrough" pain or varying types of pain. III) Stable Constant pain that does not change very much from one moment to another, and no pain-free periods. EBS: EB simplex; JEB: junctional EB; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB.

Table 2: Mean ± SD of PQAS pain parameter scores by epidermolysis bullosa (EB) subtype

	EB subtype				
	All n = 39	RDEB n = 5	DDEB n = 9	EBS n = 19	JEB n = 6
Unpleasant	4.5±3.0	6.4±3.5*	4.9±3.2**	3.5±2.6*,**	5.7±3.0
Intense	3.8±3.1	5.4±2.8*	4.7±3.4	2.4±2.4*	5.5±3.5
Tender	3.7±2.9	5.4±3.6	3.9±2.8	2.8±2.7	4.5±2.9
Surface	3.7±2.9	5.2±2.6*	4.1±3.1	2.4±2.3*	5.3±3.3
Itchy	3.5±3.5	4.8±3.3*	5.7±3.6**	2.1±2.5*,**	3.5±4.7
Sharp	3.4±3.3	5.8±2.9*	4.1±3.8	1.7±2.1*	5.3±3.8
Aching	3.4±3.2	4.4±3.2	4.4±3.4	2.6±2.7	4.0±4.3
Deep	3.4±3.1	5.2±4.0	4.6±3.3	2.4±2.5	3.5±3.4
Sensitive	3.4±2.6	4.0±2.6	4.2±2.4	2.7±2.5	3.7±3.3
Heavy	3.3±3.7	4.8±3.4	4.4±3.6	1.9±3.1	5.0±4.8

Table 2: Mean ± SD of PQAS pain parameter scores by epidermolysis bullosa (EB) subtype (continued)

	EB subtype				
Throbbing	3.0±2.9	3.8±3.6	4.3±3.0	2.4±2.6	2.3±2.9
Hot	2.8±3.0	4.6±3.9	2.8±2.9	2.2±2.5	3.0±3.9
Shooting	2.7±3.2	5.2±2.5*	3.7±3.6	1.3±2.2*	3.5±4.5
Dull	2.5±2.9	4.0±3.9	2.9±2.6	2.2±2.9	1.7±2.3
Tingling	2.5±2.8	4.0±3.4	2.4±2.5	1.8±2.2	3.7±4.3
Radiating	2.1±2.7	3.8±3.8	2.2±2.6	1.4±2.0	2.5±3.9
Numb	2.0±2.8	2.0±2.4	2.2±2.4	1.8±3.3	2.3±2.6
Electrical	1.9±2.5	2.8±3.0	1.8±1.9	1.3±1.9	3.0±4.4
Cramping	1.7±2.3	3.6±3.5	2.2±2.8	1.2±1.7	1.2±1.5
Cold	1.0±1.9	2.0±2.3	0.1±1.5	0.5±1.2	1.8±3.3

*Significant difference between recessive dystrophic EB (RDEB) and EB simplex (EBS) ($p < 0.05$).
**Significant difference between dominant dystrophic EB (DDEB) and EBS ($p < 0.05$).
Abbreviations. JEB: junctional EB; EBS: EB simplex; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB.

The time qualities for pain were selected from 3 items by multiple choice (Table 1). The most common time quality for pain was *intermittent* pain (n = 20; 74%).*Variable* pain was reported in each (sub)type (n = 5; 19%). *Stable* pain was reported only in EBS and RDEB (n = 2; 7%) (Figure 3).

DISCUSSION

The PQAS was developed to identify and score qualities of pain that cover both neuropathic and non-neuropathic types of pain. This is the first study to determine qualities of pain in EB.

Overall, the general description in EB was of *intense* pain which was experienced as *unpleasant*. RDEB patients reported pain with *tender* and *sharp* qualities; DDEB is characterized by pain with *deep* and *itchy qualities*; EBS with *sensitive* and *aching* qualities; and JEB with *surface* and *sharp* qualities.

Recently RDEB was described to include neuropathic pain qualities, further quantified by intraepidermal nerve fibre density (IENFD) testing [2]. In our study, RDEB and JEB reported similar mean scores for pathognomonic terms indicating neuropathic pain (*hot, shooting, tingling, electrical* and *cold*); higher means than EBS and DDEB on all 5 qualities. This indicates a comparable neuropathic pain mechanism in JEB, which should be quantified in order to optimize treatment of JEB pain.

With regard to pain in EB largely originating from wounds, the surface is a fitting description of pain qualities. The high intensity of pain was also seen when EB was compared with several other severe dermatological conditions using the Dermatology Life Quality Index (DLQI) survey. The *unpleasant* pain sensation was also described using the words *annoying, bothersome, miserable* and *intolerable* and is an attitude or response to pain. Pain in EB is not well understood, as the qualities of pain have never been described thoroughly. This may be the reason for the current lack of effective treatment guidelines. This is also the reason to support the reported high score attributed to *unpleasant* pain sensations in our study.

Patients with EBS reported the least severe pain profile, as can be seen clearly for virtually all pain qualities in the radar diagram (Fig. 1). The significant differences between EBS and DDEB, and EBS and RDEB highlight expected differences in pain between subtypes, as was reported in another Dutch study that referred to *bodily pain* as a parameter of the Health Related Quality of Life (HRQoL) assessment; EBS reported the least severe score followed closely by DDEB [10].

Interestingly, in our study DDEB attributed their highest score to an *itchy* pain sensation. Patients with RDEB and JEB attributed their highest

scores to a *sharp* sensation, resembling that of a *knife, spike* or *piercing*. As well as presenting clinically with a higher prevalence of open wounds than EBS and DDEB, the results suggest that JEB and RDEB pain qualities are similar.

One fascinating result seen across all EB subtypes was that a *cold* type pain scored the lowest. A recent study described cold hypersensitivity as a result of deleting the nerve circuit that codes for heat. Similar to the concept that removing heat from a room induces a cold sensation, an ablation or removal of the associated receptors (*TRPV 1*) can lead to heightened cold sensations [7]. In our results the *cold* -type pain not seen as significant in EB, can either suggest an overcompensating heat sensory circuit, or a limited or disrupted cold sensory circuit.

As the subtypes of EB are more clearly defined, it is important to maintain consistent assessments of symptoms in EB through the subdivision and independent analysis of symptoms in each EB subtype [2]. The most updated recommendations on pain management in EB successfully recognized the most effective treatment options for different painful events or circumstances, however, the recommendations were not able to acknowledge the potential for different pain qualities to predominate each EB subtype, as was seen in our study [6].

An additional question as a part of the pain survey (not conventionally included in the PQAS) allowed us to visualize the prevalence of pain per anatomical region in EB. Our findings suggest that most pain in EB is experienced in the feet, followed by the hands. An assessment of the locations of pain in EB had not previously been completed in this manner. This question was accompanied by two 2-dimensional diagrams of the human body (front and rear); however, pain symptoms in EB originating from visceral organs, bones and mucous membranes could not be reported. For future research, an EB-specific pain survey should include pain qualities and accurate anatomical localizations.

The most updated grading system for neuropathic pain research and clinical practice, maintains the importance of incorporating pain qualities into the decision-making pain classification tract [4]. These provide clinical reference points for prescription of analgesic medicines, such as gabapentin for neuropathic pain, and allow for patient-specific pain treatments.

In conclusion, the PQAS is an important tool for clinical and research assessment of pain in EB. Determining the qualities of pain, such as those that are pathognomonic for neuropathic pain, will be helpful to measure pharmacological treatment effectiveness through the deep phenotyping of pain, thus avoiding unnecessary exposure to pharmacological treatments.

ACKNOWLEDGEMENTS

We are thankful to all persons with epidermolysis bullosa who volunteerd to take part in this study of whom many shared their personal experiences of pain, one of the most difficult symptoms in today. We wish to thank Drs. José C. Duipmans, the principal point of contact for patients with EB in the Netherlands, who helped us to make this project logistically possible.

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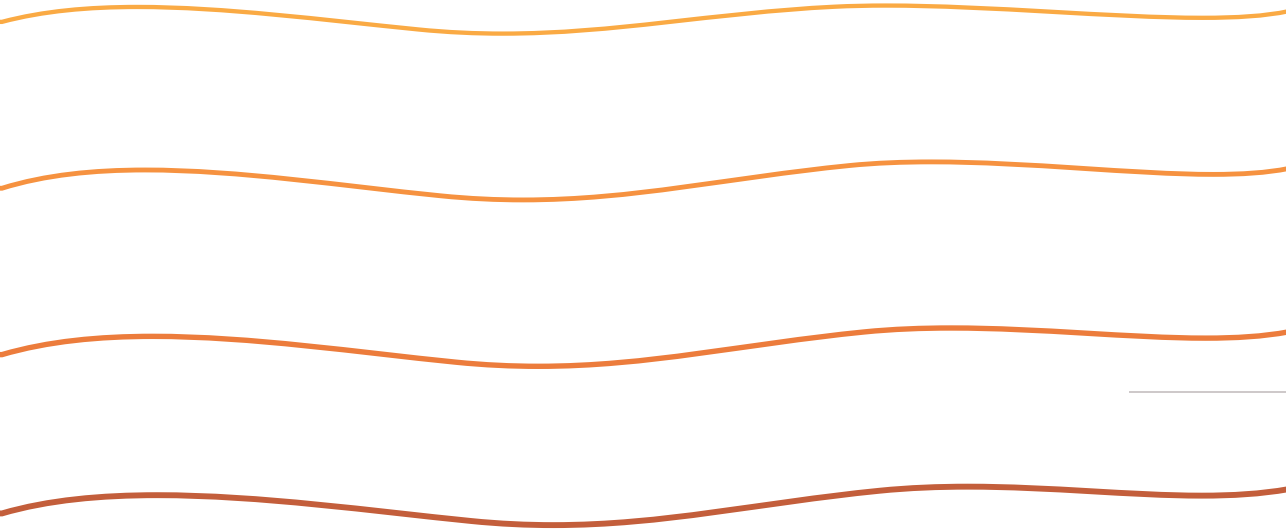
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Part II:

Exploring Cannabinoid-based Medicines



Chapter

4

Combined Tetrahydrocannabinol and Cannabidiol to Treat Pain in Epidermolysis Bullosa: A Report of Three Cases

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Br J Dermatol. 2019 Apr;180(4):922–924

ABSTRACT

Epidermolysis bullosa (EB) is a genetic blistering disorder characterized by intense pain related to disease pathology and care-based interventions. Opioid-based therapies underpin pain-care in EB however are unable to provide adequate analgesia in a significant proportion of patients. Cannabinoid-based medicines (CBMs) have been increasingly studied for pain conditions of various etiologies and pose as a novel dimension for pain-care in EB. We present three cases of EB who were prescribed pharmaceutical-grade sublingually administered CBMs comprising *tetrahydrocannabinol* (THC) and *cannabidiol* (CBD). All three patients reported improved pain scores, reduced pruritus and reduction in overall analgesic drug intake.

INTRODUCTION

Pain is the most debilitating symptom in adults with epidermolysis bullosa (EB) caused by mucocutaneous blistering, wound care and medical interventions, and in the long term is exacerbated by psychological and central sensitization. The prevalence of pain in EB is 59-93% across subtypes [5]. and leads to significant distress and poor quality of life [7]. The challenging management of pain in EB is characterised by a noteworthy consumption of pain medication. Opioids underpin EB pain-care starting as early as infancy, however are considered problematic due to developing tolerance, dependence, opioid-induced hyperalgesia, hormonal changes and obstipation. This concerns both EB patients and caregivers, and urges a pursuit for alternative treatments.

In the Netherlands, the prescription of pharmaceutical grade cannabinoid-based medicines (CBMs) containing *tetrahydrocannabinol* (THC) and *cannabidiol* (CBD) for pain has continually increased since becoming medically available in 2003 [1].

The use of CBMs for pain in EB is increasingly discussed [4]. yet remains unexplored territory. Here we report anecdotal outcomes of three EB patients suffering from refractory pain who were prescribed CBMs.

Case 1

A 64-year-old female (EB012-01) diagnosed with junctional EB generalized intermediate (JEB-gen intermed) suffered from refractory pain for over twenty years, reporting 9/10 for pain on visual analog scale (VAS). Her daily pain therapy included 3x1000mg paracetamol, 2x10mg oxycodone extended-release (ER), 1x10mg codeine-phosphate, 2x25mg amitriptyline and 1x5mg/g topical morphine (applied to the painful right heel). This regimen however, could not provide satisfactory analgesia. Ten years prior, she attempted treatment with an inhaled CBM, however experienced only short-lived analgesia (<45 minutes), and the presence of euphoria and dizziness. Subsequently an orally administered CBM-tea was prescribed with no adequate pain-relief.

Sublingual CBM-oil (20mg/ml CBD, 13mg/ml THC) was started at 0.5mg CBD and 0.325mg THC, 4x daily and increased stepwise up to 2.5mg CBD and 1.625mg THC, 4x daily. She reported VAS scores ranging between 1-4/10. At three months, she was weaned off oxycodone-ER and at six months, oxycodone immediate-release (IR) was used for dressing chang-

es only. During the following two years, treatment with topical morphine was replaced with 1mg CBD and 0.65mg THC CBM-oil, applied daily to her painful heel; she was also weaned off amitriptyline. Notably, she also reported a moderate reduction of pruritus expressed by a lower pruritus frequency and reduced urges to scratch. An increased appetite was the only side-effect reported from the CBM, and she currently maintains that this treatment provides adequate pain relief.

Case 2

A 41-year-old male (EB132-01) diagnosed with JEB-gen intermed was treated for pain, for over 10 years, with 1000mg paracetamol, 4x200mg ibuprofen, 20mg oxycodone-IR and 5mg/g topical morphine, daily. He reported a VAS for pain of 9/10 and sought alternative analgesic modalities. He was therefore started on treatment with a sublingual CBM (20mg/ml CBD, 13mg/ml THC). At one month he reached a dose of 3mg CBD and 1.95mg THC, 4x daily and reported a VAS for pain of 3/10. He was weaned off oxycodone-IR and topical morphine was stopped. Additionally after commencing the CBM treatment, he reported a reduction in the frequency and intensity of his pruritus, as well as a reduced urge to scratch. At six months due to an increase of wound-pain, supplementary treatment was started with 5mg oxycodone-IR 3x daily, subsequently inducing a self-reported distorted sense of time and delayed reaction time. On the grounds of a drug-drug interaction, the CBM was reduced to nocturnal doses only, which alleviated these symptoms and his pain relief maintained. He stopped CBM treatment two months later as his health-insurance withdrew reimbursement of the sublingual CBM-oil, which he could not afford (€200 per month). He was admitted to hospital after a subsequent exacerbation of skin ulcerations and pain, whereby his clinical team resorted to treatment with prednisolone 15mg daily for two weeks which provided only moderate analgesia. His pain treatment remains unresolved.

Case 3

A 36-year-old male (EB015-01) diagnosed with recessive dystrophic EB generalized severe (RDEB-gen sev) had a history of complications including chronic pain, pruritus, obstipation, pseudosyndactyly, squamous cell carcinoma (SCC) of his hands, and multiple amputations. His pain treatment consisted of topical morphine, oxycodone-ER, oxycodone-IR, amitriptyline, paracetamol, etoricoxib and locally injected dexamethasone. He experienced sedative side effects from amitriptyline, delayed wound-healing by topical morphine, and obstipation due to oxyco-

done-ER, oxycodone-IR and etoricoxib. Unable to tolerate these side-effects, he experimented with CBM-*flos* (the dried flower of the female cannabis plant) by way of combustion and inhalation. During routine clinical follow-up he reported an improvement of pain treated with paracetamol and inhaled CBM-*flos* and his opioid-induced obstipation resolved.

After six months, worsening tumour pain in both hands required supplementary analgesia. As EB pain recommendations indicated the use of strong opioids, which were contraindicated due to his susceptibility for side-effects, a sublingual CBM oil (20mg/ml CBD, 13mg/ml THC) was started. At one week he reported a 40% reduction in pain intensity. Both the sublingual CBM and intrapulmonary CBM were continued for two years. The combination of intrapulmonary and sublingual CBMs surpassed previous pain treatments, and additionally reduced the severity of pruritus and his urge to scratch.

Later, he entered terminal care as a sequelum of metastasized cutaneous SCC and persisted to continue both intrapulmonary and sublingual CBM administration, combined with 10mg amitriptyline and 10mg prednisolone, daily. He died at 38 years of age.

DISCUSSION

Pain in EB significantly impacts quality of life and day-to-day functioning [5,15]. In addition to nociceptive pain associated with blistering and wounds, peripheral nerve damage objectified in RDEB [2], and postulated in JEB, adds plausibility to high reported pain scores in these EB types [11]. Neuropathies limit the central role of opioids for EB-pain as they may be less effective for this type of pain according to systematic analysis [6].

The persistent inflammatory condition in RDEB skin may also contribute to central sensitization to painful stimuli [2]. which is challenging to objectify through diagnostic techniques, nor responds adequately to targeted therapies [14]. The different etiologies of pain in EB require tailored interventions and therefore pain-care is optimized through combined drug treatments and psychologocial interventions. However, the limited effectiveness of conventional analgesics stresses the fact that the gold standard for pain-care in EB has yet to be established, hence motivating

clinicians to consider alternative treatments for EB-pain from various etiologies.

All three patients were prescribed CBMs, comprising THC and CBD, by way of sublingual administration, with good effects. Two patients however, had used at least one other administration form of which one patient had administered self-acquired CBMs. Studies on CBM treatments show varying levels of success with moderate-quality evidence supporting CBM efficacy for chronic pain [13]. In general the difficulty of measuring clinical outcomes of CBM treatments is characterized by numerous administration forms and cannabinoid compositions. This has led to a call for the production and distribution of standardized, pharmaceutical-grade, CBM compositions and administration forms which can increase the predictability of dosing and effects as well as reducing the hazards of over- and underdosing, in the clinical setting [12].

Cannabinoids mimic the actions of endocannabinoids, endogenous ligands, that play a key role in synaptic transmission. Pain modulation has been a central point of discussion explained, amongst others, by the actions of cannabinoids on neuronal circuits through cannabinoid-binding receptor (CB) dependent and independent pathways [3].

CB1 and CB2 are expressed on presynaptic terminals of primary afferent pain circuits, brain areas processing nociception, including the central-medial thalamic nuclei, periaqueductal gray and raphe nuclei, and are co-localized with mu-opioid receptors in the spinal cord junction for peripheral nociceptive neurons. The role of CB2 anti-nocinception has also been implied in inflammatory and neuropathic pain models, likely due to the interaction of the endocannabinoid system with endorphin/enkephalin, vanilloid/transient receptor potential and inflammatory systems [10]. CB1/2 have been localized in human skin, and CB2 activation on keratinocytes is described to produce antinociception through the peripheral release of endogenous opioids [10].

Pruritus entails the largest physical and psychological burden for children with EB [7]. and the reported diminished frequency and intensitites of pruritus in these cases is notable as the antipruritic effects of CBMs have been postulated in several dermatologic conditions [8].

In these cases patients were prescribed the combination of THC and CBD, which are the most studied plant-based cannabinoids (phytocannabinoids). THC, like the endocannabinoids *2-arachyldonylglycerol* and *anandamide,* is a partial agonist of CB1/2 and has been shown to stimulate beta-endorphin production, allowing for opioid sparing in clinical practice [9]. CBD in contrast to THC has a low affinity for CB1/2, and at high doses does not produce psychotropic effects [10]. Interestingly CBD is able to antagonize undesired effects of THC such as sedation and intoxication whilst concurrently improving desirable effects like analgesia [10]

Although the therapeutic potential of CBMs in pain control in EB is interesting, one cannot exclude the effect of placebo on patient reported changes. In addition to this, core aspects of CBM therapeutics include the sufficient expression of CB1/2, which in EB is unknown. These limitations warrant further investigations of CBMs in controlled study settings in order to objectify the reported pain changes observed in these cases, and close the gap between current treatment standards and patient needs.

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Chapter

5

Cannabinoid Use and Effects in Patients with Epidermolysis Bullosa: An International Cross-Sectional Survey Study

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Orphanet J Rare Dis. 2021 Sep 6;16(1):377

ABSTRACT

Background: Epidermolysis bullosa (EB) patient anecdotes and case reports indicate that cannabinoid-based medicines (CBMs) may alleviate pain and pruritus and improve wound healing. CBM use has not been characterized in the EB patient population.

Objectives: To evaluate CBM use among EB patients, including CBM types, effects on symptoms (e.g., pain and pruritus), disease process (e.g., blistering, wounds, and inflammation), well-being (e.g., sleep, appetite) and concomitant medications.

Methods: English-speaking EB patients or caregivers completed an online international, anonymous, cross-sectional survey regarding CBM use. Respondents reported the types of CBMs, subsequent effects including perceived EB symptom alteration, changes in medication use, and side effects.

Results: Seventy-one EB patients from five continents reported using or having used CBMs to treat their EB. Missing question responses ranged between 0 (0%) and 33 (46%). Most used more than one CBM preparation (mean: 2.4±1.5) and route of administration (mean: 2.1±1.1). Topical and ingested were the most common routes. Pain and pruritus were reported retrospectively to decrease by 3 points (scale: 0–10; $p<0.001$ for both) after CBM use. Most reported that CBM use improved their *overall EB symptoms* (95%), *pain* (94%), *pruritus* (91%) and *wound healing* (81%). Most participants (79%) reported decreased use of pain medications. The most common side-effect was dry mouth (44%).

Conclusions: CBMs improve the perception of pain, pruritus, wound healing, and well-being in EB patients and reduced concomitant medication use. Nevertheless, a direct relation between the use of CBMs and reduction of the above-mentioned symptoms cannot be proven by these data. Therefore, future controlled studies using pharmaceutically standardised CBM preparations in EB are warranted to delineate the risks and benefits of CBMs.

BACKGROUND

Epidermolysis bullosa (EB) is a group of clinically and genetically heterogeneous genetic skin conditions whereby patients have fragile skin and mucosae that blister with slight trauma [33]. EB is characterized by repeated blistering and wounding, often with impaired wound healing, leading to a cascade of secondary problems, including chronic wounds, scarring, deformities, infections and extracutaneous symptoms [11]. EB is divided into types according to the level of blister formation, including EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB), which is further subdivided into recessive DEB (RDEB) and dominant DEB (DDEB). [33]

Pain and pruritus have a significant impact on quality of life in EB patients; two of the top three unmet needs for EB patients include effective pain and pruritus treatments [20,29,50,57]. EB patients and clinicians continually seek out novel treatments to improve symptomatic care and quality of life. Two recent case series have brought to light the use of cannabinoid-based medicines (CBMs) in the EB-care setting [16,48,66]. However, the therapeutic potential and risks of such drugs have yet to be delineated in the context of EB care.

Cannabinoids, whether endogenous (endocannabinoids), plant-derived (phytocannabinoids), or synthetic, are molecules that activate various cascading pathways through endogenous cannabinoid-binding receptors (CB1 and CB2) and transient receptor potential (TRP) ion channels within the endocannabinoid system (ECS) [56]. These receptors are ubiquitous in the central and peripheral nervous systems but are also localized to the immune system and skin [9,56,71]. Over 100 cannabinoids have been isolated, however Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and well-studied active cannabinoids [2]. THC, known for its psychoactive effects, is a partial agonist of CB1 and CB2. CBD, which is psychotropically inert, antagonizes THC effects, improving the tolerability of THC when co-administered [45].

Pain treatment with CBMs has been well-described. Literature reviews of clinical studies have shown CBMs to be tolerable, reasonable therapeutic options for chronic pain in various conditions [44,73,74]. On the contrary, the effects of CBMs on pruritus lack sufficient clinical studies, but underlying mechanisms are attributed to neuronal activation, and local effects on keratinocytes and mast cells [4,18,37,41,52]. The modulation

of pain and pruritus through CB1/CB2 ligation warrants further research on their potential role in alleviating symptoms and has the potential to become a novel target for treatment in EB [7,48].

To improve our understanding of CBM treatments currently being used in EB, and give direction to future research, we report the results of a survey aimed at highlighting patient-reported CBM-use, and self-reported effects on their EB.

PATIENTS AND METHODS

Eligibility included all types of inherited EB, all ages, and any geographic location. The survey was available online in English. Caregivers or parents could complete the survey on a patient's behalf. Participants 18 years old or older provided electronic informed consent. Assent and parental informed consent were completed for respondents aged 7 to 18 years. Parental informed consent was obtained for participants less than 7 years old.

The survey link was shared among EB-related social media groups and EB non-profit organization web pages and newsletters. Survey information was distributed among professional networks (EB Clinical Research Consortium and EB Clinical Network) who shared the information with EB patients.

The cross-sectional online survey obtained self-reported data on demographics, disease characteristics, CBM characteristics, effects of CBMs on EB symptoms, side effects, and changes in concomitant medication use. Survey questions were developed based on previously reported effects of CBMs on EB and other conditions, as well as input from EB patients and expert physicians [16,66]. As this was an internationally disseminated survey, given the potential illegality of CBMs, it was designed to uphold participant anonymity. The survey utilized skip logic whereby pertinent follow up responses could be elicited. Retrospective pain and pruritus levels pre- and post-CBM use were collected as numerical rating scales (NRS), ranging from 0-10 [39]. The Wong-Baker FACES scale was included to assist with self-reporting of pain [28]. A 5-point Likert scale was used to assess improvement or worsening of EB symptoms; a 6-point Likert scale was used to assess medication changes. Options for "Not Applicable" were included for EB symptoms and medication use. An

option to upload the CBM product label was included to confirm reported content of the product(s) used. Respondents had the option to include free text comments, which were reviewed by study staff. Qualitative answers were assessed for predominant themes.

Survey responses were collected, and data was managed using REDCap (Research Electronic Data Capture) secure electronic data capture tools hosted at Stanford University. Both the study and survey instrument were approved by the Stanford Institutional Review Board (Protocol #53145) and the Groningen Institutional Ethics Review Board. Survey responses were collected from March through August 2020.

To ensure that only unique survey completions were included, surveys with identical responses for demographics or qualitative responses were identified and reviewed; the survey with the fewest completed questions was removed. Each individual survey was reviewed to confirm that responses appeared credible. Survey respondents that reported no previous or current CBM use were excluded. Incomplete surveys were included, however those that failed to complete at least the sections on CBM characteristics were excluded.

Levels of pain and pruritus pre- and post-CBM use were compared by utilizing non-parametric tests. Non-parametric testing was also applied to group comparisons. For costs, class midpoints from ordinal responses were extracted, and foreign currencies converted to United States Dollars based on exchange rates in December 2020. Statistical analyses were performed using SPSS (version 23.0).

RESULTS

Demographics

In total, 155 surveys were returned. Of these, 84 surveys were excluded based on either incompletion (n=42), no CBM use reported (n=40), or were identified as duplicates (n=2). The remaining 71 (45.8%) survey responses comprised the analyzed study cohort (**Table 1**). Surveys were completed more frequently by EB patients (43/71, 60.6%) than parents/caregivers (28/71, 39.4%). Most responses came from North America (62/71, 87.3%) but the cohort included inhabitants of five continents. The majority were ≥18 years old (45/71, 63.4%). Participants with RDEB (37/51, 52.1%) comprised the largest represented EB type. Most partic-

ipants reported *moderate* to *very severe* EB severity (58/71, 81.7%). The vast majority of participants (62/71, 87.3%) currently used CBMs, versus those that had stopped using CBMs. Reasons for discontinuation included: CBMs were too expensive (n=4), a better medication was found (n=3), and that CBMs were illegal (n=1). The median monthly costs for CBMs were USD $75.00 (IQR $66.84–$150).

Cannabinoid-Based Medicine Characteristics

Participants reported characteristics of the CBMs administered and were able to report on multiple CBMs (**Table 2**). *Oil/paste*, *flos* and *edible* (infused or cooked into foods) were the most prevalent CBM preparations. On average, individual participants administered 2.4 (±1.5) CBM preparation types. *Topical* (36/60, 60.0%) and *ingested* (36/60, 60.0%) were the most frequently encountered routes of administration. On average, participants used 2.1 (±1.1) administration routes. More respondents (18/44, 40.9%) preferred the *inhaled* route compared to other routes. For participants under 13 years, topical administration was most frequently used (12/19, 63.2%).

Most commonly, CBM products contained both THC and CBD (41/118, 34.7%), followed by CBD-only (24/118, 20.3%) and THC-only (18/118, 15.3%). An unknown cannabinoid content was reported for 29.7% of CBMs (35/118). The largest group within respondents under 13 years used CBD-only (9/19, 47.4%).

The majority of participants (34/51, 66.7%) administered CBMs at least once daily. The largest group reported that their dose of CBM fluctuated over time (17/52, 32.7%), followed by both stable and increased (13/52, 25.0%), and decreased (6/52, 11.5%). For frequencies of CBM usage, most participants reported either *stable* or *fluctuating* (17/52, 32.7%) frequencies.

CBMs were acquired primarily through dispensaries (31/50, 47.0%) and social connections (19/50, 28.8%). A minority of CBMs were prescribed (12/50, 24.0%), however most participants (28/50, 73.7%) reported that their clinicians were aware of their CBM use. Within the group of 12 participants using prescribed CBMs, 9 were from the United States, 2 from the Netherlands, and 1 from Australia.

Reasons for initiating CBM use were reported by 63 patients as a qualitative open-ended response. Of these responses, the most cited reason to

start using a CBM was to treat pain (n=40), and other EB symptoms, such as wound healing (n=11), to improve sleep (n=5), and to treat pruritus (n=5). Additionally, respondents reported starting CBM as an alternative to opiates (n=8), inadequate control with non-CBM regimen (n=7), and intolerable side effects for non-CBM regimen (n=6).

Reported Effects of Cannabinoid-Based Medicines

Statistically significant reductions in self-reported pain and pruritus were reported retrospectively following CBM use (median pain change-score: -3, IQR: -2 to -4 [p<0.001, 95% CI: 2.95-4.04], median pruritus change-score: -3, IQR: -1.25 to -5 [p<0.001, 95% CI: 2.59-3.10]) (Figure 1). There were no significant differences in the change scores for pain and pruritus between EB types (pain: p=0.837, pruritus: p=0.864) or self-reported disease severity (pain: p=0.644, pruritus: p=0.962). As most participants reported multiple CBM routes of administration and formulations, it was not possible to analyse degrees of improvement based on these variables.

The vast majority of participants reported improvement (*much improved* or *a little improved*) in *overall symptoms* (46/48, 95.8%), *overall pain* (45/48, 93.8%) and *overall pruritus* (40/44, 90.9%) from CBM administration (Figure 2). To a lesser extent, *skin inflammation* (34/47, 72.3%) and *wound healing time* (29/48, 60.4%) were reportedly improved with CBMs.

Within effects specific to pain types and qualities, most participants reported improvements in *background pain* (39/41, 95.1%), *pain related to movement* (38/42, 90.5%), *pain located at wounds* (39/46, 84.8%), *pain during dressing changes* (35/42, 83.3%) as well as *itchy* (41/43, 95.3%), *shooting* (31/36, 86.1%), *stabbing* (31/35, 88.6%) and *burning* (30/36, 83.3%) qualities of pain.

The *ability to relax* (41/43, 95.3%), *overall mood* (36/39, 92.3%), *improvement in anxiety* (32/36, 88.9%), *sleep* (39/43, 90.7%), and *ability to move around* (37/43, 86%) were the most frequently improved effects related to participants' well-being.

Of participants who reported having skin cancer (n=10), two indicated reduced cancer growth. Of the seven who reported experiencing pain from skin cancer, six (85.7%) denoted decreased pain from skin cancer with CBM use.

Notably, a small fraction of responses indicated worsening in *overall symptoms* (1/48, 2%), *overall pruritus* (1/44, 2.3%), *wound infections* (1/44, 2.3%), *pain during dressing changes* (1/42, 2.4%), *pain with an itchy quality* (1/43, 2.3%), *pain in the mouth/throat* (1/31, 3.2%), *appetite* (1/40, 2.5%), and *energy levels* (5/41, 12.2%) (**Figure 2**).

Effects of CBM administration on pain and pruritus treatments were highlighted by cessation of, or reduction in the use of, opioids (12/15, 80.0%), over the counter pain medications (18/23, 78.3%) and anti-itch medications (17/25, 68.0%, **Figure 3**). Of participants who required wheelchair assistance, most (14/25, 56.0%) reported a reduced need to use a wheelchair.

The most commonly encountered side-effect from CBM administration was *dry mouth* reported by 44% of participants (Table 2). *Cough/wheezing* (29%), and *dry/red eyes* (27%) were the next most prevalent side effects.

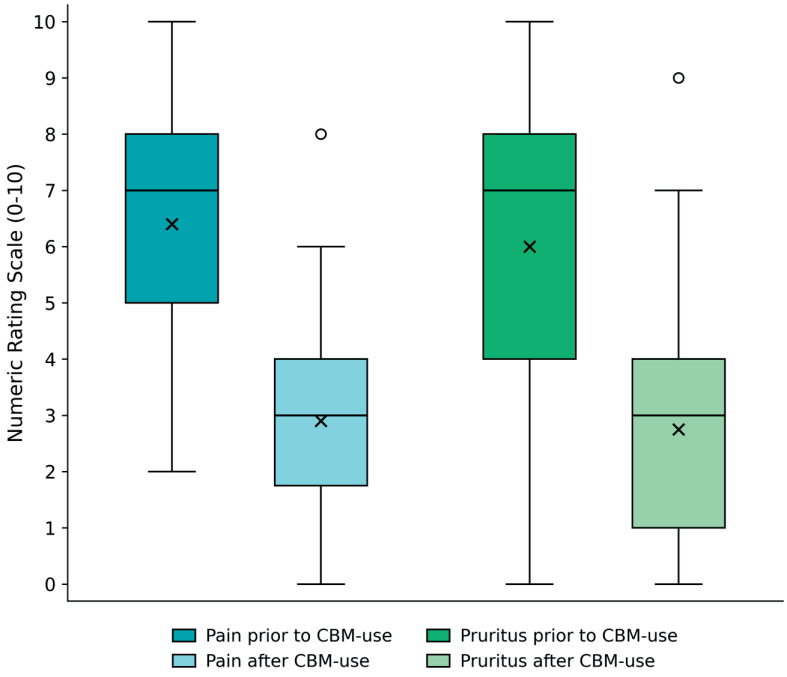


Figure 1: Boxplot of numeric rating scale (NRS 0-10) scores for pain and pruritus prior to- and after cannabinoid-based medication (CBM) administration. Note the improvement in the perception of both pain and pruritus following CBM use. Significant differences ($p<0.001$) were seen for changes in pain and pruritus (*prior to CBM-use* versus *after CBM-use*)

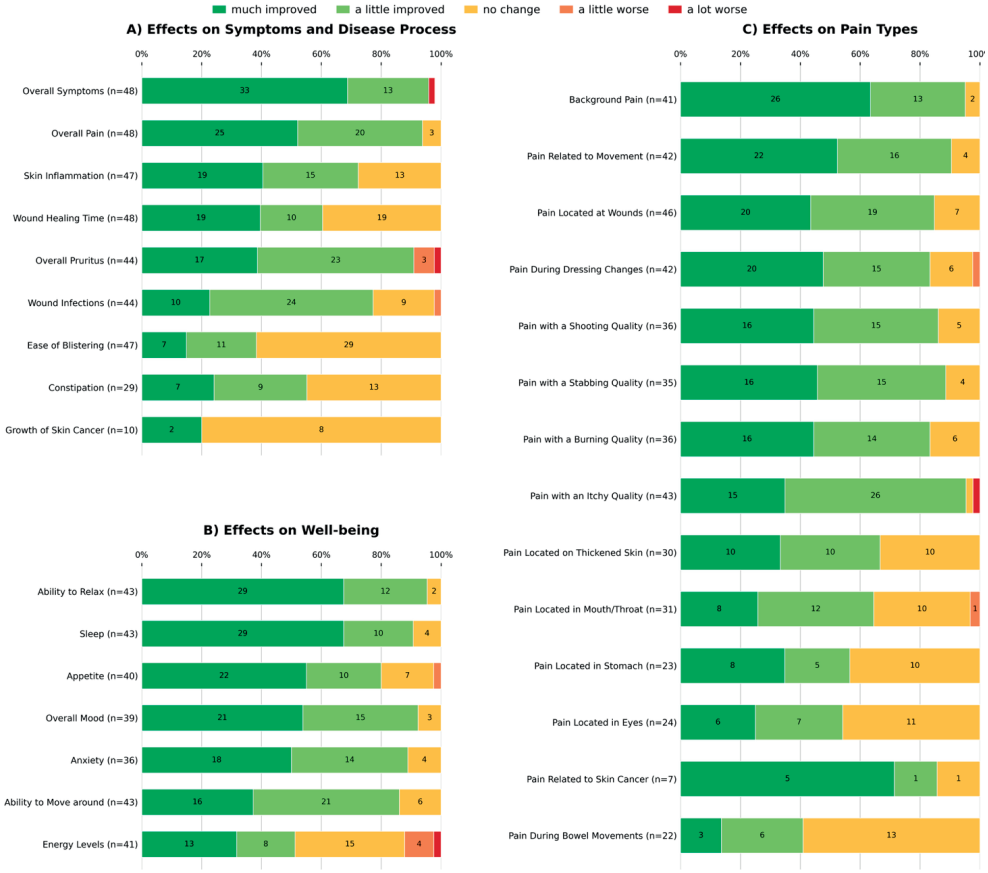


Figure 2: Participant-reported effects of cannabinoid-based medicines on epidermolysis bullosa-related (A) symptoms and disease process, (B) well-being and (C) pain types. Data is ordered by frequency of *much improved*. N=48 responses are included. Items indicated as *not applicable* by participants are removed

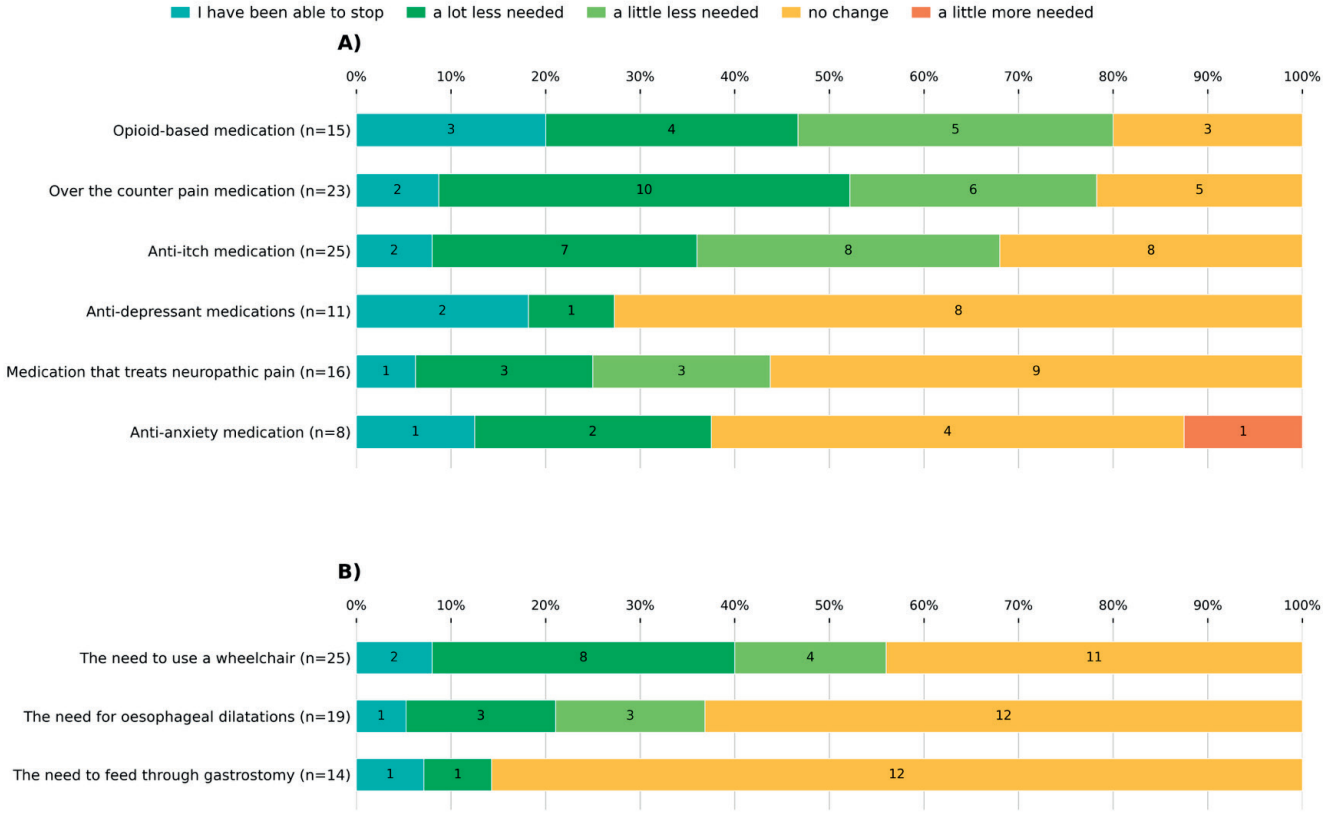


Figure 3: **A**) Reported changes in pain and pruritus treatments due to cannabinoid-based medication administration. **B**) Reported changes in supportive interventions. Note that not all participants answered each question. No participants indicated "A lot more needed" for any responses.

Table 1: Demographics, participant reported EB characteristics and CBM-use status of survey respondents (n=71), grouped by EB types. One participant with unknown EB type was removed from EB type columns. [RDEB: recessive dystrophic epidermolysis bullosa, DDEB: dominant dystrophic epidermolysis bullosa, EBS: epidermolysis bullosa simplex, JEB: junctional epidermolysis bullosa, CBM: cannabinoid-based medicine, IQR: inter-quartile range, USD: United States dollar.

	Total Cohort	RDEB	DDEB	EBS	JEB
Participants Enrolled, n (%)	71 (100.0)	37 (52.1)	8 (11.3)	17 (23.9)	8 (11.3)
Participant Role, n (%)					
Patient	43 (60.6)	18 (48.6)	6 (75.0)	13 (76.5)	5 (62.5)
Parent/Guardian/Caregiver	28 (39.4)	19 (51.4)	2 (25.0)	4 (23.5)	3 (37.5)
Age, n (%)					
<7	11 (15.5)	5 (13.5)	1 (12.5)	3 (17.6)	2 (25.0)
7-12	8 (11.3)	7 (18.9)	-	1 (5.9)	-
13-17	7 (9.9)	7 (18.9)	-	-	-
18-25	10 (14.1)	7 (18.9)	3 (37.5)	-	-
26-34	14 (19.7)	6 (16.2)	1 (12.5)	5 (29.4)	2 (25.0)
>34	21 (29.6)	5 (13.5)	3 (37.5)	8 (47.1)	4 (50.0)
Sex, n (%)					
Male	40 (56.3)	25 (67.6)	4 (50.0)	7 (41.2)	3 (37.5)
Female	31 (43.7)	12 (32.4)	4 (50.0)	10 (58.8)	5 (62.5)
Geographic Region, n (%)					
North America	62 (87.3)	33 (89.2)	7 (87.5)	16 (94.1)	5 (62.5)
Europe	5 (7.0)	2 (5.4)	1 (12.5)	1 (5.9)	1 (12.5)
Oceania	2 (2.8)	1 (2.7)	-	-	1 (12.5)
Asia	1 (1.4)	1 (2.7)	-	-	-
Africa	1 (1.4)	-	-	-	1 (12.5)
Self-reported Severity, n (%)					
Very mild	1 (1.4)	-	-	1 (5.9)	-
Mild	12 (16.9)	2 (5.4)	3 (37.5)	7 (41.2)	-
Moderate	22 (31.0)	9 (24.3)	3 (37.5)	6 (35.3)	3 (37.5)
Severe	24 (33.8)	18 (48.6)	1 (12.5)	3 (17.6)	2 (25.0)
Very Severe	12 (16.9)	8 (21.6)	1 (12.5)	-	3 (37.5)
CBM-use, n (%)					

Table 1: Demographics, participant reported EB characteristics and CBM-use status of survey respondents (n=71), grouped by EB types] (*continued*)

	Total Cohort	RDEB	DDEB	EBS	JEB
Currently administering CBM	62 (87.3)	33 (89.2)	6 (75.0)	14 (82.4)	8 (100.0)
Previously administered CBM	9 (12.7)	4 (10.8)	2 (25.0)	3 (17.6)	-
Age when CBM started, median (IQR)	19 (14.0-26.0)	16 (11.8-24.3)	18 (10.0-21.5)	25 (12.5-38.0)	25.5 (21.8-44.5)
Monthly Costs in USD, median (IQR) (n=49)	$75.00 ($66.84-$150)	$117.33 ($75.00-$150.00)	$112.50 ($33.42-$150.00)	$75.00 ($27.15-$150.00)	$75.00 ($25.00-$91.93)

Table 2: Reported cannabinoid-based medicines (CBMs) and characteristics of administration in the total cohort. * Indicates that participants were able to select more than one response. Participants were not required to respond to each item. Administration by way of suppositories were not reported by any participant. [THC: delta-9-tetrahydrocannabinol, CBD: cannabidiol]

Survey Item Subject (number of responses to item)	Multiple Choice options for Survey Responses	All Respondents (%)	Respondents <13 years (%)
CBM Type* N All Respondents = 60 N <13y = 19	Oil/Paste	46 (76.7)	11 (57.9)
	Dried Flower/Flos	33 (55.0)	2 (10.5)
	Edible	29 (48.3)	2 (10.5)
	Tincture	17 (28.3)	3 (15.8)
	Other liquid form	11 (18.3)	1 (5.3)
	Pill	5 (8.3)	-
	Total CBM Types Used	141	19
	Mean per participant	2.4 (±1.5)	1.0 (±0.7)
CBM Route of Administration* N All Respondents = 60 N <13y = 19	Topical	36 (60.0)	12 (63.2)
	Ingested	36 (60.0)	4 (21.1)
	Inhaled	33 (55.0)	-
	Sublingual	23 (38.3)	4 (21.1)
	Total Routes Reported	128	20
	Mean per participant	2.1 (±1.1)	1.1 (±0.8)

Table 2: Reported cannabinoid-based medicines (CBMs) and characteristics of administration in the total cohort. (*continued*)

Survey Item Subject (number of responses to item)	Multiple Choice options for Survey Responses	All Respondents (%)	Respondents <13 years (%)
Topical CBM Type* N All Respondents = 36 N <13y = 19	Cream	24 (66.7)	8 (42.1)
	Oil	23 (63.9)	6 (31.6)
	Lotion	12 (33.3)	4 (21.1)
	Spray	3 (8.3)	1 (5.3)
	Foam	-	-
	Total Types of Topicals	62	19
	Mean per participant	1.7 (±1.1)	1.1 (±1.2)
Composition of CBM (THC vs. CBD)* N All Respondents = 58 N <13y = 19	THC only	18 (15.3)	-
	THC/CBD combination	41 (34.7)	6 (31.6)
	CBD only	24 (20.3)	9 (47.4)
	Unknown	35 (29.7)	4 (21.1)
	Total Compositions Reported	118	19
Current Frequency of CBM Administration N All Respondents = 51 N <13y = 10	Less than once per week	5 (9.8)	2 (20.0)
	Once per week	2 (3.9)	-
	Several times per week	8 (15.7)	1 (10.0)
	Once per day	15 (29.4)	4 (40.0)
	Several times per day	19 (37.3)	2 (20.0)
	Unsure	2 (3.9)	1 (10.0)
Change over time: Dose of CBM N All Respondents = 52 N <13y = 11	Dose decreased	6 (11.5)	1 (9.1)
	Dose remained stable	13 (25.0)	2 (18.2)
	Dose increased	13 (25.0)	4 (36.4)
	Dose fluctuated	17 (32.7)	2 (18.2)
	Unsure	3 (5.8)	2 (18.2)

Table 2: Reported cannabinoid-based medicines (CBMs) and characteristics of administration in the total cohort. (*continued*)

Survey Item Subject (number of responses to item)	Multiple Choice options for Survey Responses	All Respondents (%)	Respondents <13 years (%)
Change over time: Frequency of CBM Administration N All Respondents = 52 N <13y = 11	Administered less frequently	7 (13.5)	1 (9.1)
	Frequency remained stable	17 (32.7)	3 (27.3)
	Administered more frequently	9 (17.3)	2 (18.2)
	Administration frequency fluctuated	17 (32.7)	4 (36.4)
	Unsure	2 (3.8)	1
CBM Source of Acquisition* N All Respondents = 50 N <13y = 10	Cannabis dispensary	31 (62.0)	6 (60.0)
	Social connection	19 (38.0)	2 (20.0)
	Internet web-shops	6 (12.0)	4 (40.0)
	Medical pharmacy	5 (10.0)	1 (10.0)
	Cultivated at home	4 (8.0)	-
	Prefer not to answer	1 (2.0)	-
	Total Number of Sources	66 (100)	13 (100)
Preferred Route of Administration N All Respondents = 44 N <13y = 9	Topical	11 (25.0)	4 (44.4)
	Inhaled	18 (40.9)	
	Ingested	10 (22.7)	2 (22.2)
	Sublingual	5 (11.4)	3 (33.3)
Duration of Use N All Respondents = 52 N <13y = 11	<6 months	13 (25.0)	5 (45.5)
	6 months – 1 year	7 (13.5)	4 (36.4)
	1 – 5 years	18 (34.6)	2 (18.2)
	>5 years	14 (26.9)	-
Reported Side Effects* N All Respondents = 45 N <13y = 9	Dry mouth	20 (44.4)	-
	Cough/wheezing	13 (28.8)	-
	Dry/red eyes	12 (26.7)	1 (11.1)
	Fatigue	10 (22.2)	-
	Dizziness	7 (15.6)	-
	Paranoia	3 (6.7)	-
	Problems with memory/attention	3 (6.7)	-
	Problems with coordination	3 (6.7)	-

Table 2: Reported cannabinoid-based medicines (CBMs) and characteristics of administration in the total cohort. (*continued*)

Survey Item Subject (number of responses to item)	Multiple Choice options for Survey Responses	All Respondents (%)	Respondents <13 years (%)
CBM Prescribed by Physician N All Respondents = 50 N <13y = 10	Yes	12 (24.0)	1 (10.0)
	No	38 (76.0)	9 (90.0)
Physician Aware of CBM Use N All Respondents = 50 N <13y = 9	Yes	28 (73.7)	7 (77.8)
	No	10 (26.3)	2 (22.2)

DISCUSSION

We report the first international summary of patient reported CBM use in EB. The literature assessing CBM treatments in EB is non-existent. To date only two small (n=6 total) retrospective case-series have been published, which highlighted various cannabinoid compositions of CBMs, administered topically or sublingually [16,66]. The reported effects here were strikingly similar, characterized by reductions in pain, pruritus, and in the use of other systemic medications, such as opioids. In EB, pain treatment guidelines have noted the use of CBMs as potential modalities, but evidence remains empirical [29].

EB is an immensely burdensome condition from birth, which, in the absence of a cure or highly effective treatments, means that patients are on a continuous journey to find relief in novel, repurposed or alternative treatments [60]. It is not surprising that EB patients willingly experiment with treatments that may not have been thoroughly investigated, such as CBMs that contain CBD and THC. Several participants reportedly sought out CBMs as an alternative to conventional medications (such as opioids), or other substances (such as alcohol). Reassuringly the majority informed their clinicians of their CBM use. However, even with promising anecdotes, before any clinical decisions can be made regarding their safety, tolerability and effectiveness, CBM treatment risks and benefits should be clearly delineated.

Most of the responses in this study were from North America, despite international outreach to recruit respondents; four other continents were also represented. Due to the extensive availability of CBMs in the United States and Canada, it was fitting that the majority of responses originated from these two countries [12,40].

The vast majority of respondents had RDEB, and half of participants reported their EB as *severe* or *very severe*. Although each EB type has a unique pathophysiology, some symptoms, such as blistering and wound formation, overlap. Patients with any EB type can perceive their disease as severe, influenced by environmental and psychosocial factors; it appears that this perception of disease severity likely contributed to participant willingness to try CBMs [13]. However, reported improvement in symptomatology was not exclusive to RDEB, nor was it seen only in patients who self-classified as *severe*.

The most commonly cited reason for discontinuing CBMs was price, with an average of USD $75 spent monthly. A downside to the burgeoning market of CBM products is the expense, especially in a population already significantly impacted by the financial burden of caring for their disease [3,31]. Notably, some participants in the United States reported that they started using CBMs due to difficulties in obtaining conventional allopathic medications, either due to price, lack of insurance coverage, or difficulty obtaining prescriptions (often narcotics).

Characteristics of Cannabinoid-Based Medicines

The administration routes reported in this study were predominantly inhaled, topical and oral, closely followed by sublingual. Generally, inhaled and sublingual CBM administration lead to the fastest plasma cannabinoid peaks, due to the direct absorption of cannabinoids into the vasculature, allowing for efficient dose-titration in shorter time-frames [38,43]. This may partially explain why participants in this study mostly preferred the inhaled route.

Topical CBMs, however, have local effects, whereby psychotropic or systemic side-effects are very limited, but the mechanisms of peripheral CB1/2 binding may differ from systemic CBMs [36]. Patients or caregivers may initiate these CBM treatments due to the ease of topical administration, the high burden of skin related problems in EB, and the desire to minimize side effects, as was reported in a case study [16]. We found that topical administration of CBD-only products were the predominant CBMs

used for children with EB. The increased availability of legal CBD-only products may have also contributed to the increased use of these products compared to other CBMs.

Most participants administered CBMs at least daily, underscoring the degree of intervention required to manage EB symptoms. The reported dosages and frequency of use showed heterogeneity in change over time. A small, yet significant number of participants noted an increase in both administered dose (13/52, 25%) and administration frequency (9/52, 17.3%) over time. Typically, tolerance to the efficacy of CBMs containing THC and CBD, has not been observed.[6,61,63,67] However, tolerance is developed to known effects from cannabinoid receptor agonism such as impaired neurocognition and cardiovascular changes [19]. The changes in dose and frequency of administration seen in this study may also be due to the dynamic natural history of symptoms in EB, such as the development or resolution of blistering and chronic or recurrent wounds, fluctuations in pain and pruritus, or disease progression, amongst an array of factors [11,70].

There is ongoing debate as to the synergistic value of combining multiple cannabinoids (i.e., both CBD and THC) in CBM treatments [64]. The phytocannabinoids THC and CBD, amongst other cannabinoids, have unique binding properties with CB1/2 and other ECS-associated receptors. THC is proposed as the molecule central to CBM pain treatments, however current recommendations include adding CBD to mitigate THC-mediated side effects [26]. Increasing ratios of THC:CBD linearly improve patient-reported effects for numerous indications, but could reduce these effects at too high a ratio [15]. The varying cannabinoid compositions used by participants in our study may be due to differences in legality, availability, recommendations from peers, or settings where participants acquired CBMs. Standardizing CBM compositions, as well as finding the optimal ratios for such treatments will help gain more accurate insights into CBM effects in EB.

Effects on Symptoms of Epidermolysis Bullosa

Both the highest prevalence and proportion of reported improvement from CBMs was in *overall symptoms*. This was closely followed by *overall pain* and *pruritus*. As participants indicated multidimensional positive effects of CBMs in this study, it is likely that the synergistic improvements in multiple aspects of their disease may together be more clinically

meaningful than each individual effect. Contrastingly, very few patients reported worsening of symptoms.

The greatest degrees of improvement were observed in *background pain*, *pain related to movement* and *wound pain*. Some of the most well studied indications for CBM interventions are chronic pain conditions [5,74]. The consistently superior results of CBMs, containing both THC and CBD, versus placebo in non-EB neuropathic pain studies is promising, but is overshadowed by lack of high-quality evidence [53]. To date, CBMs have, at most, moderate quality evidence supporting their effectiveness for chronic pain. Pain, however, is a complex experience, influenced by neurobiological and psychosocial mechanisms [24]. The aetiology of pain in EB can be multifactorial including nociceptive pain (e.g., acute wounds, chronic wounds, dressing changes, surgical interventions, and extra-cutaneous sites of tissue damage), continuous background pain, neuropathic and nociplastic pain [29]. Due to the heterogeneity of pain mechanisms and responses to CBMs, establishing therapeutic mechanisms of CBMs in EB will be a challenging feat, but one deserving of additional study.

Many respondents reported overall reductions in pruritus. Patient-centred research has shown that pruritus is one of the most bothersome symptoms in EB [20,65,68]. Despite numerous treatment modalities, alleviation is challenging [21,57]. Thus, pruritus relief by way of intervention with CBMs could be especially meaningful to patients. Decreased pruritus was also noted in the previous case report of sublingual CBM use in EB patients [66]. However, one patient in our study did note increased pruritus as a side effect of CBMs. CBMs have reportedly decreased pruritus in multiple conditions such as atopic dermatitis, psoriasis, prurigo nodularis, uremic pruritus, and lichen amyloidosis [4,62]. It is postulated that the anti-pruritic actions of CBMs, like in pain, are due to effects within the ECS including ligation of CB1/2 receptors, and TRP channel modulation [4,18,52]. Additional studies are warranted to investigate pruritus alterations with CBMs in EB, including elucidating the most effective routes of administration, and CBM compositions.

The wound environment in EB consists of an interplay between intrinsically impaired wound healing, bacterial colonization, inflammation and the external wound environment [32]. The majority of participants reported improved wound healing and inflammation from CBMs. After tissue injury, the ECS plays an intricate role in the regulation of cytokines,

nitrergic signalling and keratinocyte differentiation, through direct and indirect activation of cannabinoid receptor ligands [18,46,54,72]. The two recent case series, coupled with our results deem further investigation necessary to address whether CBM modulation of the ECS is beneficial for EB wounds [16,66]. We do note that subjectively reported improvements in wound healing and inflammation could also be multifactorial, secondary to reductions in pain and/or pruritus. The natural history of EB wounds is often unpredictable and influenced by both biological and environmental factors [69,70]. Future studies assessing the effects of CBMs on EB wounds should incorporate objective wound assessments.

The highest proportions of reductions in concomitant medications were seen in opioid-based analgesics, over the counter analgesics, and anti-itch medications. These treatments comprise one aspect of the multidimensional approach to symptomatic care in EB [29,57]. Yet, often in EB, conventional medications do not provide adequate effectiveness and are eclipsed by their burdensome short and long term side-effect profiles [29,30]. Identifying effective pain and pruritus treatments remains a research priority in EB [13,14,22,23]. Recent reviews suggest a prominent opioid-sparing effect from CBMs, warranting future clinical studies to investigate a causal relationship [55]. Although CBMs do not appear to alter the human pharmacokinetics of opioids, the ECS and endogenous opioid systems share neuroanatomical, neurochemical and pharmacological characteristics [1,8]. The reduction of concomitant analgesic and anti-pruritic medication in this study seems promising, and mirror those effects previously reported wherein some patients were able to discontinue opioids [16,66]. However, it is of significant importance to obtain a clear picture of this phenomenon in EB by clarifying both the short and long-term risks and benefits of these medication regimen alterations.

Notably, of the respondents who required a wheelchair, more than half were able to decrease or even stop using their wheelchair. These respondents reported both improved *energy levels* and *ability to move around*. It is likely that these improvement are related to the reduction in symptomatic burdens, yet remains an important finding as increased mobility in EB has myriad conceivable benefits [17,35,49].

Ten participants reported skin cancer, of which two noted a reduction in growth with CBMs. There have been reports of anti-neoplastic effects of CBMs [51,52,71]. Unfortunately, we are not able to validate these findings, nor can we describe potential anti- or pro-neoplastic effects

of CBMs, as no conclusive evidence has delineated the mechanisms of action, risks and benefits of such therapies in EB. Additionally, 6/7 participants reported reduced pain from skin cancer (the type of cancer was not specified), due to CBMs. Current literature suggests a role for CBMs in alleviating cancer-related pain in non-EB patients, however high quality evidence is lacking [10].

A large proportion of participants indicated a positive impact of CBMs on their well-being, of which the greatest reported improvements were for the *ability to relax* and *sleep*. Daily well-being has been given substantial consideration in EB best practice guidelines, and highlight the multidimensional burdens of living with EB [29,47]. Whether these reported improvements are direct physiological effects of CBMs, or indirect through symptom alleviation, are not known and will require further investigation.

Side Effects

In this study, dry mouth was the most commonly reported side-effect, likely due to inhibition of salivation through CB1/2 modulation in the salivary glands, via THC and CBD-induced agonism [59]. Dry eyes were also reported, probably through similar mechanisms in lacrimal glands. Ocular, oral, and dental sequelae of EB can be exacerbated by these effects, and thus should be considered prior to CBM administration [25]. However, overall, scientific literature points out that CBMs are generally well tolerated, as was reported by participants in this study [27].

An additional factor to consider, with specific regard to THC, is CBM dependence and withdrawal symptoms after therapy cessation, or periods of cessation, which were not incorporated in this study. The lifetime risk for dependence after cannabis use in recreational settings (high THC concentrations and aim to achieve psychotropic effects) is 8.9% [42]. The dependence risk whilst using CBMs for therapeutic goals is however unknown. Withdrawal symptoms may include irritability, anger, anxiety, sleep difficulty, decreased appetite and weight loss, and is dose-dependent [75]. Future prospective controlled studies taking withdrawal into account, may add value to the sparse evidence on withdrawal after clinically supervised CBM-use.

Limitations

Given the potential illegality of CBM use, we implemented an anonymous online survey. Thus, we were unable to gauge the prevalence of CBM use, nor a response rate. During the data cleaning phase, the research team cross-checked individual responses, but could not completely validate the content of submitted surveys.

The number of included patients was small for English speaking countries outside North America and may be due to differences in availability of CBMs. Unfortunately, we must also accept that CBM use, even with clinical supervision, carries a stigma whereby patients may refrain from disclosing their use.

The composition of the CBM products used by patients is also not entirely clear. While we attempted to ascertain the cannabinoid compositions of CBMs by allowing participants to upload product labels, not every participant uploaded their label. Additionally, the commercial market regarding CBMs remains unregulated whereby cannabinoid compositions are non-standardised and may be inaccurately labelled [34,58]. In order to avoid health risks of accidentally administering unwanted additives, it is important for patients to acquire CBMs from reputable sources. This also underscores the potential benefit of regulation which would come with legalization of CBM products.

Furthermore, we unfortunately were unable to determine how cannabinoid concentrations (CBD versus THC) and route of administration contributed to the perceived efficacy of CBMs reported in this study, as most participants used multiple products and routes of administration. Additional areas of future exploration include those that were alluded to by free text comments. Various participants reported that certain formulations and routes may be more efficacious for different symptoms and scenarios: “We find that a combination of ingested and topical applications works best, as each product helps with a different aspect of EB. Ingested products help with internal inflammation and pain control. Topical products help with localized pain and wound healing.” Certainly, additional controlled studies are warranted to explore the complex relationships between cannabinoid compositions, routes of CBM administration, EB (patho-)physiologies and symptoms.

Finally, we recognize that there may have been a selection bias as the responses may comprise patients reporting very positive or very negative experiences. The retrospective reporting methodology makes this study vulnerable to a recall bias, and is also cause to interpret the findings with caution. Furthermore, these experiences are not standardized and there is a possibility that participants are benefitting from a placebo effect, underscoring the need for future controlled studies.

CONCLUSION

In conclusion, this study highlights the use and perceived multidimensional beneficial effects of treatments with CBMs by EB patients on EB symptoms and disease process. Future prospective controlled clinical studies are warranted to elucidate the potential role of CBMs in EB treatment.

ACKNOWLEDGEMENTS

The authors are indebted to the Epidermolysis Bullosa Research Partnership, Epidermolysis Bullosa Medical Research Foundation, Epidermolysis Bullosa Clinical Research Consortium, Dystrophic Epidermolysis Bullosa Research Association International, Dystrophic Epidermolysis Bullosa Research Association United States, Dystrophic Epidermolysis Bullosa Research Association Canada, and CLINET. We would also like to thank the EB patients and their caregivers who completed our survey.

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APPENDIX

CBM & EB Survey

Stanford University (US) & University Medical Centre Groningen (NL)

Throughout this survey, the terms 'cannabis' or 'cannabis products' refer to cannabis, marijuana, THC, CBD, and all cannabinoid products. It may be helpful to have your product packaging available when completing this survey.

Section 1: About You

Who is completing this survey?

- ☐ EB patient
- ☐ Parent / guardian / caregiver on behalf of EB patient

Age of EB patient:

- ☐ 0–6 years
- ☐ 7–12 years
- ☐ 13–17 years
- ☐ 18–25 years
- ☐ 26–34 years
- ☐ 35 years or older

Sex of EB patient:

- ☐ Male
- ☐ Female
- ☐ Other
- ☐ Prefer not to answer

Country of residence:

Country

If in the United States, please specify your state:

State

Is cannabis legal where you live?

- ☐ Legal for medical use only (prescribed by a doctor)
- ☐ Legal for recreational use
- ☐ Legal for both medical and recreational use
- ☐ Not legal
- ☐ I don't know
- ☐ Other

EB subtype:
- □ Recessive Dystrophic EB (RDEB)
- □ Dominant Dystrophic EB (DDEB)
- □ Junctional EB (JEB)
- □ EB Simplex (EBS)
- □ Kindler Syndrome
- □ I don't know
- □ Other

How severe do you consider your EB?
- □ Very mild
- □ Mild
- □ Moderate
- □ Severe
- □ Very severe

Section 2: Cannabis Use

Do you currently use cannabis for your EB?
- □ Yes
- □ No

Have you ever used cannabis for your EB?
- □ Yes
- □ No

If you have stopped using cannabis, when did you stop?
- □ Less than 6 months ago
- □ 6 months – 1 year ago
- □ 1–5 years ago
- □ Over 5 years ago

If you stopped, why? (select all that apply)
- □ Too expensive
- □ Illegal in my country
- □ Could not use at work / school
- □ Adverse effects
- □ Did not help my EB
- □ Found a better medication
- □ Other

Why did you decide to start using cannabis?

Section 3: Product Type and Route of Administration

What type(s) of cannabis products have you used? (select all that apply)
- □ Flower (e.g. marijuana, leaf, bud)
- □ Oil or paste (e.g. vape pen, topical oil)

- ☐ Edible (e.g. food, brownie)
- ☐ Pill (e.g. tablet, capsule)
- ☐ Drink (e.g. tea)
- ☐ Tincture
- ☐ Suppository
- ☐ Other

By what route(s) have you used cannabis? (select all that apply)

- ☐ Topical (applied to the skin — oil, cream, spray, lotion, foam)
- ☐ Inhaled (smoked or vaporised)
- ☐ Ingested / swallowed (edibles, drink, pill)
- ☐ Sublingual (under the tongue — tincture, oil, spray)
- ☐ Suppository (rectal or vaginal)
- ☐ Other

For each route used, please provide product details where known:

Complete only the rows relevant to your use. You may attach product labels if available.

For topical use: where do you apply it? (select all that apply)

- ☐ To wounds
- ☐ To unwounded skin
- ☐ To painful thickened skin (keratoderma)
- ☐ Other

Which route of administration do you prefer?

- ☐ Topical
- ☐ Inhaled
- ☐ Ingested
- ☐ Sublingual
- ☐ Suppository
- ☐ Other

Please describe your preference or any additional comments:

Section 4: Frequency and Duration of Use

How long have you used cannabis?

- ☐ Less than 6 months
- ☐ 6 months – 1 year
- ☐ 1–5 years
- ☐ Greater than 5 years

How often do you use cannabis?

- ☐ Less than once per week
- ☐ Once per week

- ☐ Several times per week
- ☐ Once per day
- ☐ Several times per day
- ☐ Other

Approximately how old were you when you first started using cannabis medicinally?

Age (years)

Has the amount you use per session changed over time?

- ☐ Decreased
- ☐ Stayed the same
- ☐ Increased
- ☐ Fluctuated
- ☐ Don't know

Has the frequency of your cannabis use changed over time?

- ☐ Less frequent
- ☐ Stayed the same

Route	Brand name	THC %	CBD %	THC:CBD ratio	Dose per use	Units
Topical						
Inhaled						
Ingested						
Sublingual						
Suppository						
Other						

- ☐ More frequent
- ☐ Fluctuated
- ☐ Don't know

Section 5: Procurement

Where do you obtain your cannabis? (select all that apply)

- ☐ Cannabis dispensary / store
- ☐ Pharmacy (medical prescription)
- ☐ Social connection / friend
- ☐ Internet / web shop
- ☐ Grown at home
- ☐ Prefer not to answer
- ☐ Other

How much do you spend per month on cannabis products (approximate)?

- □ 0–50
- □ 50–100
- □ 100–200
- □ 200–500
- □ 500–1000
- □ >1000
- □ I don't know

Currency (e.g. USD, EUR, GBP):

Is your cannabis prescribed by your doctor?

- □ Yes
- □ No

Does your doctor know that you use cannabis?

- □ Yes
- □ No

Section 6: Effects on Pain

Please rate your overall average daily pain from EB BEFORE cannabis use (0 = no pain, 10 = worst possible):

Before cannabis:	0	1	2	3	4	5	6	7	8	9	10

Please rate your overall average daily pain from EB AFTER cannabis use:

After cannabis:	0	1	2	3	4	5	6	7	8	9	10

In general, how has cannabis affected your EB symptoms?

- □ Gives me great relief
- □ Gives me a little relief
- □ Makes no difference
- □ I feel a little worse
- □ I feel a lot worse

What effect has cannabis had on the following types of pain?

N/A = not applicable / I don't have this type of pain

Section 7: Effects on Skin

What effect has cannabis had on the following?

N/A = not applicable / I don't have this problem

	Much improved	A little improved	No change	A little worse	A lot worse	N/A
Overall pain	☐	☐	☐	☐	☐	☐
Pain from blisters or wounds	☐	☐	☐	☐	☐	☐
Pain from thickened skin (keratoderma)	☐	☐	☐	☐	☐	☐
Itchy pain	☐	☐	☐	☐	☐	☐
Burning pain	☐	☐	☐	☐	☐	☐
Shooting pain	☐	☐	☐	☐	☐	☐
Stabbing pain	☐	☐	☐	☐	☐	☐
Pain during dressing changes	☐	☐	☐	☐	☐	☐
Pain caused by movement (e.g. walking)	☐	☐	☐	☐	☐	☐
Background / constant pain	☐	☐	☐	☐	☐	☐
Eye pain	☐	☐	☐	☐	☐	☐
Mouth / throat pain	☐	☐	☐	☐	☐	☐
Pain when defecating	☐	☐	☐	☐	☐	☐
Stomach pain	☐	☐	☐	☐	☐	☐
Pain from skin cancer	☐	☐	☐	☐	☐	☐
Itchiness / pruritus	☐	☐	☐	☐	☐	☐
Wound healing time	☐	☐	☐	☐	☐	☐
Ease of blistering	☐	☐	☐	☐	☐	☐
Skin inflammation	☐	☐	☐	☐	☐	☐
Wound infections	☐	☐	☐	☐	☐	☐
Growth of skin cancer	☐	☐	☐	☐	☐	☐

Please rate your overall average daily itch BEFORE cannabis use (0 = no itch, 10 = worst possible):

Before cannabis:	0	1	2	3	4	5	6	7	8	9	10

Please rate your overall average daily itch AFTER cannabis use:

After cannabis:	0	1	2	3	4	5	6	7	8	9	10

Section 8: Effects on Wellbeing

What effect has cannabis had on the following?

N/A = not applicable / I don't have this problem

	Much improved	A little improved	No change	A little worse	A lot worse	N/A
Appetite	□	□	□	□	□	□
Constipation	□	□	□	□	□	□
Ability to move around (e.g. walk)	□	□	□	□	□	□
Overall mood	□	□	□	□	□	□
Anxiety	□	□	□	□	□	□
Ability to relax	□	□	□	□	□	□
Sleep	□	□	□	□	□	□
Energy levels	□	□	□	□	□	□

Please describe any other effects cannabis has had on your wellbeing:

Section 9: Concomitant Medication Use

Did you take any of the following medicines around the same time you used cannabis?

Medication	Currently using	Used in past
Over-the-counter pain medicines *e.g. paracetamol, ibuprofen, aspirin*	□	□
Opioid pain medicines *e.g. oxycodone, tramadol, morphine, codeine*	□	□
Neuropathic pain medicines *e.g. gabapentin, pregabalin, amitriptyline*	□	□
Anti-itch medicines *e.g. hydroxyzine, loratadine, cetirizine, ondansetron*	□	□

Medication	Currently using	Used in past
Anti-depressants *e.g. duloxetine, fluoxetine, sertraline, mirtazapine*	□	□
Benzodiazepines / anti-anxiety medicines *e.g. lorazepam, diazepam, alprazolam*	□	□

For each medication used, how did your need change after starting cannabis?

Answer only for medications you used.

Medication	Able to stop	A lot less needed	A little less needed	No change	A little more needed	A lot more needed
OTC pain medicines	□	□	□	□	□	□
Opioid pain medicines	□	□	□	□	□	□
Neuropathic pain medicines	□	□	□	□	□	□
Anti-itch medicines	□	□	□	□	□	□
Anti-depressants	□	□	□	□	□	□
Benzodiazepines	□	□	□	□	□	□

Do you use or have you used any of the following?

	Yes	No
Esophageal dilations	□	□
Gastrostomy tube (G-tube)	□	□
Wheelchair or walking assistance device	□	□

If applicable: please describe any change in need for the above after starting cannabis:

Section 10: Side Effects

Did you experience any of the following side effects from cannabis?

Side effect	Yes	No	Don't know
Paranoia	□	□	□
Dizziness / lightheadedness	□	□	□
Fatigue	□	□	□
Problems with coordination	□	□	□
Problems with memory or attention	□	□	□

Side effect	Yes	No	Don't know
Dry mouth	□	□	□
Dry or red eyes	□	□	□
Cough / wheezing	□	□	□
Nausea / vomiting	□	□	□
Hallucinations / psychosis	□	□	□

Please describe any other side effects:

Section 11: Closing Questions

Would you recommend cannabis to other EB patients?

□ Yes
□ No
□ Prefer not to answer

Where do you get your information about medicinal cannabis?

Do you have any questions or recommendations for the scientific community?

Any other comments about cannabis and EB?

Thank you for completing this survey.

Chapter

6

Protocol

The C4EB Study — Transvamix® (10% THC/5% CBD) to Treat Chronic Pain in Epidermolysis Bullosa: A Protocol for an Explorative Randomized, Placebo-Controlled, Double-Blind Crossover Study

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PLoS One. 2022 Dec 12;17(12):e0277512

ABSTRACT

Introduction:

Patients with the genetic blistering skin condition epidermolysis bullosa (EB) report severe pain as a consequence of skin and mucous membrane lesions including blisters, wounds, and scars. Adequate symptom alleviation is not often achieved using conventional pharmacologic interventions. Finding novel approaches to pain care in EB is imperative to improve the quality of life of patients living with EB. There are several anecdotal reports on the use of cannabinoid-based medicines (CBMs) by EB patients to reduce the burden of symptoms. Controlled clinical investigations assessing these reported effects however are lacking. As the pain quality "unpleasantness" delineates EB pain, we hypothesize the modulation of affective pain processing in the brain by way of intervention with CBMs comprising the cannabinoids Δ-9-tetrahydrocannabinol and cannabidiol - objectified by functional magnetic resonance imaging (fMRI).

Methods:

The C4EB study is an investigator-initiated, single-centre, randomized, double-blind, placebo-controlled and crossover trial. Adult patients with the genetic diagnosis epidermolysis bullosa, reporting chronic pain will be eligible to participate. Following baseline measurements, participants will be randomized to receive the sublingually administered interventions placebo and Transvamix® in forward or reversed orders, each for two weeks and separated by a washout.

The primary outcome is the difference in numeric rating scale pain scores between grouped interventions, using affective descriptors within the Short-form McGill Pain Questionnaire-2. Secondary outcomes include pain self-efficacy, concomitant analgesic medication-use and adverse events. Additionally, fMRI will be employed to assess brain connectivity related to neuroanatomic pain circuits at baseline, placebo and Transvamix® interventions.

The study was approved by the ethical committee at the University Medical Center of Groningen in the Netherlands. Results will be submitted for publication in peer-reviewed journals.

INTRODUCTION

Patients with the genetic blistering skin condition, epidermolysis bullosa (EB), report a significant impact on quality of life compared to other skin conditions [38]. EB is considered a rare disease with an incidence and point-prevalence in the Netherlands of 41.3 per million live births and 22.4 per million population, respectively [2]. Amongst adults with EB, pain is the most debilitating symptom initially caused by blistering, chronic wounds, skin contractures and neuropathies [10]. Persistent pain in EB becomes a complex multidimensional experience due to psychosocial, and emotional components [6,7,11,26]. Due to this complex nature of pain in EB, adequate analgesia is difficult to achieve, leading to chronic refractory pain. In a recent cross-sectional study on EB in the Netherlands, patients with all EB-types rated "unpleasant" pain quality as the highest score of 20 qualities of pain [31]. This is interesting as research has shown that pain affect, located in the limbic system, which can be reported as the pain quality "unpleasantness", is functionally distinct from sensory discriminative pain processing pathways [27]. One way to analyse pain affect is using functional magnetic resonance imaging (fMRI) techniques to measure brain connectivity in known and suspected neuroanatomical areas processing pain affect [8,15,27]. Research groups applying this technique have identified the amygdala and anterior cingulate cortex (ACC) as central brain areas with altered connectivity during chronic pain. Furthermore, independent of the aetiology of chronic pain, all chronic pain states (measured by fMRI) show similarities in altered brain connectivity, sometimes referred to as neuronal reorganization, which can be subsequently reversed with effective treatments [16].

Endogenously produced cannabinoids (endocannabinoids) play a key role in the modulation of pain signals by binding endocannabinoid receptors 1 and 2 (CB1/2) [3,18]. CB1/2 are ubiquitous in the human body, however CB1 is most prevalently found in the central nervous system with the exception of lower brain-stem regions for cardiovascular and respiratory functions - explaining the unattainable lethal doses and complete absence of mortality from exogenous cannabinoid administration [17,23,37]. As CB1/2 are densely populated in the frontal-limbic areas of the brain, their role in modulating pain affect has been proposed [22]. Like these endocannabinoids, exogenous cannabinoids, namely delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), also target these receptors, modulating neurotransmitter release in the CNS. Specifically, the amygdala and ACC are shown to have altered functional connectivity

to brain cortices through CB1/2 agonism [22]. This change in connectivity significantly correlates with a decrease in the pain, and more specifically, a decrease in the pain quality "unpleasantness" from noxious stimuli after systemic administration of exogenous cannabinoids, most often derived from the plant (phytocannabinoids) [5,22,34]. In recent years, clinical studies on various painful diseases have shown the superiority of combining multiple cannabinoids compared to single-cannabinoid extracts, with specific regard to the combination of THC and CBD [28–30]. This is likely attributed to an improved tolerance of THC-based interventions, by way of paradoxical CBD CB1/2 receptor antagonism [28,30].

It is important to note that the use of cannabinoid-based medicines (CBM) for pain, often as self-medication, have preceded clinical studies and sufficient clinical evidence. Given the limited effectiveness of conventional treatments in EB, it is well-known that these patients have used CBMs for symptom alleviation and have subsequently reported promising anecdotes. A recent study collected data on 71 EB patients around the world using CBMs. Although the cohort mainly comprised patients with a more severe EB, all EB-types described symptomatic improvements. A considerable obstacle to interpreting these experiences is the significant variability in administration forms, cannabinoid compositions, and doses used by patients. Additionally, these products are often not regulated as pharmaceutical products and therefore lack pharmaceutical-grade standardisation and quality control. However, seventeen of the participants administered CBMs sublingually and retrospectively reported mean NRS (0–10) pain reductions of 3.58 (±1.8) after administering CBMs [32].

In the Netherlands, CBMs are produced and compounded by companies overseen by the Dutch government and have been available on prescription since 2003. From 2015 CBM oils comprising THC and CBD in varying ratios have been empirically prescribed to several Dutch patients with EB [24]. Good quality evidence on CBM effectiveness in EB, and mechanisms of action, remain elusive. Nevertheless, clinical studies on heterogenous chronic pain conditions show moderate evidence for the efficacy of CBMs (comprising THC and CBD) versus placebo [1,36].

To date, it has also been shown that neither the dose administered nor detected plasma levels of cannabinoids are good predictors of pain alleviation when treated with CBMs. The high inter-individual variability (CV%) is likely due to patient variations in BMI, enterohepatic circulation, degradation in the gut, previous cannabinoid exposure, the endogenous

cannabinoid system (endocannabinoid system) compositions and differences in administration technique [12,19].

Therefore, the current best-practice is for patients administering CBMs to undergo dose-escalation titration following a premeditated dosage build-up scheme (e.g., administration 4x daily). In order to achieve an effective dose, patients continue titration until side-effects are reached, and subsequently reduce their dose by one step in the titration scheme, and subsequently maintain this dose [9]. Methods for dose-escalation vary significantly between patients in clinical practice, which is why a fixed titration scheme should be employed for research studies. This feasibly standardizes the dose-escalation for all participants in clinical studies, individualizing the dose-required but standardizing the method to achieve this. Controlled studies in rare diseases, like EB, encounter several hurdles including small population sizes, high participation burden and ethical dilemmas related to placebo administration. To address these, the proposed study allows for participation with unchanged medication regimens already in place and employs a crossover methodology where participants will receive both placebo and the chemically active intervention for a short period of time.

Taken together, the unmet treatment needs for pain in EB and moderate quality evidence for the use of CBMs to treat pain and modulate pain affect, open grounds for further clinical investigation. To substantiate this research avenue, CBM interventions in EB, the proposed explorative study will gain insight into effects of Transvamix®, a sublingually administered and standardized CBM, on pain, brain connectivity, doses achieved through titration and adverse events. New fMRI techniques to assess brain connectivity enhance the assessment of both baseline connectivity characteristics in EB patients with pain, as well as connectivity changes in areas processing pain affect. In the clinical research setting it is therefore imperative to standardize dose-escalation schemes, administer standardized pharmaceutical grade CBMs, apply validated patient reported outcomes, and employ sufficient sample sizes and rigorous statistical analyses. We hypothesize a novel avenue of pain intervention for EB by modulating pain affect – objectified by fMRI. (1079 words)

METHODS AND ANALYSIS

Design and setting

The study design is an explorative, randomized placebo-controlled and double-blind intervention crossover study: Transvamix® (100mg/mL THC / 50mg/mL CBD) to treat chronic pain in Epidermolysis Bullosa. This is an explorative study because cannabinoid-based medicines (CBMs), Transvamix-like drugs, have not yet been studied by way of controlled trials in the EB patient population. The addition of placebo mitigates confounding participation bias. The crossover design reduces the number of participants required, an important factor when studying rare diseases, and supported by randomization and blinding, enables rigorous statistical analyses. In addition to this, effects of group outcomes on a group level can be analysed. Participant inclusion will commence in Q4 of 2022 for a period of 6 months. Study completion is expected in Q4 of 2023. After completion, analysis will be performed whereby results publication is expected in Q4 of 2023.

Inclusion, exclusion and randomization

Participants in this study are adult patients with a confirmed diagnosis (genetic testing, immunofluorescent diagnostics, or electron microscopy) of inherited epidermolysis bullosa (EB). All patients with EB in the Netherlands are registered at the Dutch Expertise Centre for Blistering Diseases, Department of Dermatology, University Medical Centre Groningen. To participate, patients must be currently living in the Netherlands and are at least 16 years of age. Participation is not limited to one sex, nor to any ethnic group. Written informed consent will be obtained and stored in a locked cabinet at the research centre.

Eligible participants, who have consented to participation, will undergo inclusion screening at the research centre. Subjects must meet all the following criteria (Table 1). The Trial Master File will be maintained by Felix Farma B.V. They will also manage blinding of participant data, as well as randomization and allocation. An a priori randomization code generator will be completed before the start of inclusion, for the total expected number of participants. Participants will be allocated to groups receiving intervention in the orders T-P or P-T (T=Transvamix; P=Placebo). Confirmation of participant inclusion will be recorded in the eCRF. Either Transvamix® or placebo will be delivered by courier to participants 3 days before the allocated commencement of treatment administration.

Instructions for administration are provided both verbally and in writing to participants.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Clinical diagnosis, supplemented by genetic analysis, immunofluorescent diagnostics, or electron microscopy of congenital epidermolysis bullosa (EB).
At least 16 years of age from the date inclusion.
Can read and write in the Dutch language.
Mentally competent and legally able to appreciate informed consent.
Reporting an average pain mean score ≥4 on NRS (0-10) averaged throughout the previous week at one of the following times of day: morning, afternoon, or evening.
Exclusion criteria
Patients enrolled in other clinical trials that do not allow for a deviation in treatment.
Have experienced myocardial infarction or clinically significant cardiac dysfunction within the last 12 months or have had a cardiac disorder that, in the opinion of the investigator would have put the participant at risk of a clinically significant arrhythmia or myocardial infarction.
Patients with known psychotic disorder (including the use of antipsychotic medications), or a history of suicidal ideation.
Female patients of child-bearing potential and male participants whose partner was of child-bearing potential, unless willing to ensure that they or their partner used effective contraception.
Patients who have had significantly impaired renal or hepatic function in the last 12 months.
The patient is currently using or has used cannabis or cannabinoid-based medications within 30 days of study entry and was unwilling to abstain for the duration of the study.
Patients unwilling or unable to refrain from driving road vehicles and/or using potentially dangerous machinery where sufficient concentration is necessary, during the study period.
Patients unable to stay within the Netherlands for the duration of the study period.
History of addiction and/or hospital admission due to addiction to recreational or pharmaceutical drugs.
Patients with contraindications for MRI determined using the MRI safety form pertaining to for example, surgical, cosmetic, or accident-related metal objects in/on the body; claustrophobia.

Intervention: Transvamix® and placebo

The investigational medicinal product (IMP) is Transvamix®, a cannabinoid-based medicine (CBM) comprising 100mg/mL THC (delta-9-tetrahydrocannabinol) and 50mg/mL CBD (cannabidiol) (Transvamix-oil THC 10% / CBD 5%, 10ml). Transvamix® is prepared by Felix Farma B.V.

using pharmaceutical-grade cannabis produced by Bedrocan B.V., and isolated using an ethanol-based extraction process. The product, Transvamix®, has a standardized cannabinoid composition within regulatory margins. The placebo formulation is comparable in texture, colour, and taste. Identical packaging and labelling will be used. Both Transvamix® and placebo will be administered using a 1 ml syringe.

Participants will receive both the IMP (Transvamix®) and placebo in forward (T→P) or reverse (P→T) orders, depending on treatment arm allocation after randomization (Fig 1). The study drugs (Transvamix® and placebo) will be provided by Felix Farma B.V. A washout of two weeks between both interventions, based on cannabinoid metabolite half-lives, will mitigate carry-over effects.

Transvamix® and placebo are administered sublingually using a 1 millilitre dosing syringe.

All participants will follow the predetermined titration scheme (Table 2). The titration will be stopped at the onset of side-effects (as reported by the participant), and the dose administered reduced by one day in the titration scheme. This will be called the sub-side effect threshold maintenance dose.

This achieved dose will be maintained for the remaining intervention period until day 14 is completed for each intervention (Transvamix® and placebo). Both placebo and IMP (Transvamix®) will undergo the same titration scheme. The maximum dose is 0.75ml/day Transvamix® or placebo (divided between 4 separate administrations). See Table 2 for the titration period.

Drug safety

Transvamix® is produced by the Transvaal pharmacy as a compounded medication and prescribed to patients with refractory symptoms, of which pain is the most prevalent indication. CBM-oil prescriptions have been filled out over 100,000 times to patients in the Netherlands between 2015 and 2020 [25]. Since their appearance on the market 52 adverse events related to sublingually administered CBMs (of which 1 was serious: hypoglycaemia) have been reported to the centre for pharmacovigilance (LAREB) [4].

Safety monitoring

Although risk for serious adverse events is estimated to be low, a data safety monitoring board (DSMB) will be compiled, consisting of four independent members with expertise in: clinical pharmacology, longitudinal research statistics, EB clinical care, and pain/cannabinoid research. The DSMB will maintain an overview of (serious) adverse events and offer independent advice for premature completion or termination of the study.

Care as usual

Participants will continue treatments, including analgesic regimens, according to their current prescriptions and EB breakthrough pain guidelines [11] – which include instructions for breakthrough symptoms. The IMP is not intended for breakthrough symptoms as participants will adhere to a strict dosing regimen. During the baseline visit participants will report all currently used systemic treatments. Participants will report changes in dosing or additional administration to these medications (for example, breakthrough medication) in the participant's logbook.

Follow-up and data collection

Study data were collected and managed using REDCap electronic data capture tools hosted at the research centre [13,14]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Participants will receive URLs to access the surveys for online completion from a smartphone, tablet, or computer.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or non-compliance.

Primary outcome measures

The primary outcome is the change score for numeric rating scale (NRS) values using the affective descriptors from the short-form McGill Pain Questionnaire 2 (SF-MPQ2). This will be measured as the grouped difference in mean NRS scores pre- (baseline) and post- intervention (Transvamix® vs. placebo).

Secondary outcome measures

The secondary outcomes will include data derived from other patient reported outcome measurements (PROM). These outcomes will be measured as grouped differences, change scores, in mean pre- (baseline) and post-intervention (Transvamix® vs. placebo) scores. The instruments used are the SF-MPQ2 and Pain Self Efficacy Questionnaire (PSEQ) comprising NRS values. Additionally, change scores for global pain and pruritus will be measured using visual analogue scales (VAS 0-100).

Functional MRI data pertaining to brain connectivity will be analysed between placebo and Transvamix® groups. The frequency and participant reported burden (NRS 0-10, where 0 is "no burden whatsoever", and 10 is the "highest burden possible") of side-effects will be reported and compared between Transvamix® and placebo.

Lastly, analgesic medication changes, of currently used medications reported at baseline, will be reported by participants at the end of each intervention. Reductions in- or increased used will be quantified and compared between intervention groups.

Figure 1: Schedule of enrolment, interventions, and assessments (SPIRIT figure).

Participation duration: 64 days, or 9 weeks and 1 day. Duration of participant exposure to interventions: 14 days (placebo), 14 days (Transvamix®). DN-4: douleur neuropathique 4, CSI: central sensitization inventory, PCS: pain catastrophizing scale, SF-MPQ2: short form McGill pain questionnaire 2, PSEQ: pain self-efficacy questionnaire, VAS Pa/Pr: visual analogue scale pain/pruritus, fMRI: functional magnetic resonance imaging.

	STUDY PERIOD					
	Enrolment and allocation	Baseline Measurements (Before Intervention)	Post-allocation			Follow-up
TIMEPOINT ($t_{day\ number}$)	$<t_{-7}$	t_{-7} – t_0	$t_1 - t_{14}$ *Intervention*	$t_{15} - t_{28}$ *Washout*	$t_{29} - t_{42}$ *Intervention*	t_{55}
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation	X					
INTERVENTIONS:						
Transvamix® → *Placebo*			X		X	
Placebo → *Transvamix®*			X		X	
ASSESSMENTS:						
DN-4		X				
CSI		X				
HADS		X				
PCS		X				
SF-MPQ2		X	X		X	
PSEQ		X	X		X	
fMRI		X	X		X	
Toxicology			X		X	
Semi-structured Interview						X

Table 2: Titration scheme employed by study participants

Transvamix® (100mg/mL THC and 50mg/mL CBD) and **Placebo**					Total (ml)	Total THC (mg)	Total CBD (mg)
Day	06:00-09:00	11:00-14:00	16:00-19:00	21:00-00:00			
1	-	-	-	0,05 ml	0,05	5	2,5
2	-	-	-	0,05 ml	0,05	5	2,5
3	0,05 ml	-	-	0,05 ml	0,1	10	5
4	0,05 ml	-	0,05 ml	0,05 ml	0,15	15	7,5
5	0,05 ml	0,05 ml	0,05 ml	0,05 ml	0,2	20	10
6	0,05 ml	0,05 ml	0,05 ml	0,1 ml	0,25	25	12,5
7	0,1 ml	0,05 ml	0,05 ml	0,1 ml	0,3	30	15
8	0,1 ml	0,05 ml	0,1 ml	0,1 ml	0,35	35	17,5
9	0,1 ml	0,1 ml	0,1 ml	0,1 ml	0,4	40	20
10	0,1 ml	0,1 ml	0,1 ml	0,15 ml	0,45	45	22,5
11	0,15 ml	0,1 ml	0,1 ml	0,15 ml	0,5	50	25
12	0,15 ml	0,1 ml	0,15 ml	0,15 ml	0,55	55	27,5
13	0,15 ml	0,15 ml	0,15 ml	0,2 ml	0,65	65	32,5
14	0,2 ml	0,15 ml	0,2 ml	0,2 ml	0,75	75	37,5

MRI data acquisition

Whole-brain fMRI blood oxygen-level dependent data will be acquired on a 3T Siemens Magnetom Prisma with a 64-channel head coil at the Cognitive Neuroscience Centre in Groningen (https://bscs.umcg.nl/nl/faciliteiten/cognitive-neuroscience-center/), using a multi-echo echo-planar T2*-weighted imaging sequence with 550 volumes (voxel size of 2.5 × 2.5 × 2.5 mm^3 [21]. A high-resolution T1-weighted anatomical image will also be obtained (voxel size: 1×1×1 mm^3). An experienced MRI technologist will examine all structural images to ensure the absence of structural abnormalities in the brain. In case of an abnormality, the participant will be referred to their general practitioner for further examination or referral.

Sample size

We performed a sample size calculation based on data (n=28) from a recent study in Dutch patients with EB who had pain scores >3. In 28 patients, mean NRS pain scores were 5.76 ± 1.45 [33].

i. To establish a significant reduction in pain scores of 30%, with a power of 80% and a 0.05, the minimum sample size is 9 (or 5 participants in each study arm)
ii. To establish a significant reduction in pain scores of 50%, the minimum sample size is 5 (or 3 participants in each study arm).

Owing to the rarity of EB and the strict inclusion criteria for age and chronic pain, the estimated feasible participant recruitment number is 16. For this study we aim to include 16 participants (8 in each study arm).

Data handling

All data will be recorded in the eCRF REDCap, completed by either the researcher or participant, when prompted. Data will be handled confidentially and accordingly to the European guidelines for privacy protection (AVG). Research participants will be pseudonymized, personally traceable data removed, and will be identified using a participation number. Data will be stored for a minimum of 15 years after study closure.

Data analysis

Primary and secondary outcomes will be presented using descriptive statistics (means and standard deviations, or median and interquartile ranges), and subdivided into three groups (baseline, placebo and Transvamix®). The change scores for baseline to placebo and Transvamix® will be computed and incorporated for statistical testing. Visual inspection of data and a Shapiro Wilk test will be used to check for normality. Next either t-testing (paired and independent samples t-testing) or non-parametric tests (including Wilcoxon signed rank test) will be used depending on the distribution observed. The significance level will be set to $p<0.05$. In addition, mixed effects models will be applied, allowing for analysis of longitudinal data, missing data, and possible period effects.

The resting-state multi-echo fMRI dataset will be preprocessed using the ME-ICA pipeline (https://me-ica.readthedocs.io/en/latest/) [20,21]. ME-ICA uses multi-echo independent component analysis to perform motion correction and slice-time correction of the original dataset. The resulting preprocessed datasets will then be analyzed using the Matlab-based CONN toolbox (https://web.conn-toolbox.org; RRID:SCR_009550) [35]. To study the effects of Transvamix® we will primarily perform a seed-based correlation analysis, to determine the functional connectivity between the seed regions, the anterior cingulate cortex (ACC) and amygdala, and other areas in the brain. Changes in brain connectivity (baseline vs.

Transvamix® vs. placebo) will be explored in individual participants and on the group level. The neural effects of the intervention will be correlated against primary and secondary outcome measures.

CONCLUSION

In summary this explorative study will assess the use of pharmaceutical grade CBMs comprising THC and CBD in patients with EB suffering from chronic pain. The controlled cross over design of the study minimizes the burden of participation and maximizes the methodological reproducibility by employing standardized interventions and objective research outcomes. Both the chosen methodology and eventual results highlight a novel research avenue and will cornerstone future clinical research in EB and CBMs.

ACKNOWLEDGEMENTS

The authors would like to acknowledge former department head and pioneer in (pre-) clinical epidermolysis bullosa scientific research, prof. dr. M.F. Jonkman, who initiated this research avenue and drafting of the study design.

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Chapter

7

Research Letter

Sublingual Tetrahydrocannabinol and Cannabidiol to Treat Pain in Epidermolysis Bullosa: A Randomized, Placebo-Controlled Crossover Study

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Br J Dermatol. 2026;194(6):1170–1173

DEAR EDITOR,

epidermolysis bullosa (EB) comprises rare inherited skin disorders marked by extreme fragility and blistering [9]. Pain management remains a major challenge, as reported by patients and clinicians [7]. Traditionally, EB pain has been attributed primarily to nociceptive mechanisms from mechanical and inflammatory skin/mucosal stress. However, conventional nociceptive-targeted treatments, such as opioids, are frequently ineffective, leading to tolerance and significant side effects [3].

EB pain likely involves mixed nociceptive, neuropathic, and nociplastic components, with prominent unpleasantness closely aligning with the pain affect subdomain (emotional dimension of pain), contributing to suffering, burden, and limited analgesic efficacy [1,8]. Cannabinoid-based medicines (CBMs) can be effective in chronic pain conditions through modulation of pain affect pathways, observed in functional magnetic resonance imaging studies (fMRI) [10].

To date, evidence on CBMs in EB is limited to a few case reports and surveys showing positive perceptions and meaningful pain improvements [4,6]. To address this gap, we published the trial protocol[8] and conducted a randomized, double-blind, placebo-controlled, crossover trial of a standardized sublingual CBM targeting pain affect in adults with EB in the Netherlands (EudraCT: 2021-000103-20) [5]. Patient feedback informed the study design, and Felix Farma supplied the active drug and matched placebo (identical in taste, smell, colour, and consistency).

Care as usual, including analgesic regimens were continued and participants proceeded to intervention phases with either placebo or CBM containing 100 mg/mL tetrahydrocannabinol (THC) and 50 mg/mL cannabidiol (CBD), as follows: 2-week baseline, 2-week titration, 2-week washout and crossover [5]. Treatment periods were kept short to minimise burden in this exploratory study, as well as analgesia expected between 7-14 days.

Sample size (n=9) was calculated to achieve 80% power (α=0.05) to detect a 30% improvement in pain affect (relative minimal clinically important difference [MCID][2]). As an exploratory study, no absolute MCID was targeted beyond this threshold.

We included nine participants of which one withdrew early on due to a protocol violation. Eight adults (5 female; age 16–75) with EB simplex (n=4), junctional (n=3), and dominant dystrophic EB (n=1) and baseline pain ≥4/10 NRS completed the study (table 1). No participants had recessive dystrophic EB (RDEB), in contrast to prior research showing this subtype predominates among CBM users [6]. Participants were randomized 1:1 to receive study interventions in either forward or reversed orders. Participants were de-randomized following their final visit, with data unblinding performed only after completion of all statistical analyses of primary and secondary outcomes using descriptive, sign tests [5].

The primary endpoint was a 30% reduction in the *pain affect* subscale of the Short-form McGill Pain Questionnaire 2 (SF-MPQ-2). Secondary endpoints included other SF-MPQ-2 subscales, pain self-efficacy (PSEQ), concomitant analgesic use, dose of CBM achieved, and adverse events (AE). Additional validated questionnaires (DN4, HADS, PCS, CSI) were completed at baseline to characterize the study population. Urine toxicology confirmed intervention compliance as well as absence of study drug during placebo.

For CBM, the median titration dose, administered 4x daily, was reached in 7 days (25^{th}–75^{th} percentiles: 4–14 days; IQR=10 days), equivalent to 30mg THC and 15mg CBD daily, compared to 14 days (25^{th}–75^{th} percentiles: 14–14 days; IQR=0) for placebo. The results for the primary endpoint showed no statistically significant improvement in pain affect when CBM was compared with placebo. Clinically meaningful (≥30%) reduction in *pain affect* occurred in 3/8 on CBM and 3/8 on placebo. However, during CBM intervention 6/8 (75%) of participants achieved *global pain* reduction ≥30% (a summation of all pain subscales), compared to 4/8 (50%) during placebo. Other subscales within the SF-MPQ-2 (*neuropathic, intermittent* and *continuous pain*) showed no statistically significant changes. Additionally, no differences in PSEQ were observed for CBM (p=0.35) or placebo (p=0.50).

During CBM intervention, half of all concomitant analgesics reported, including oxycodone, were discontinued (n=4, 50%). During placebo intervention all analgesics were used as reported during baseline. In total 27 AEs were recorded (CBM: n=20, placebo: n=7) and were either mild (n=18) or moderate (n=9) and resolved quickly.

According to the trial protocol, resting-state fMRI aimed to assess responder and non-responder differences in pain-related brain networks. Unfortunately, due to fMRI contraindications, only a subgroup (n=3) participants underwent baseline and post-intervention fMRI preventing meaningful analysis of brain network changes. Results demonstrated considerable heterogeneity between participants and after CBM intervention. fMRI was feasible and well tolerated in EB, and can be implemented in future, larger, controlled studies.

Despite growing patient- and clinician-reported benefits of CBMs in EB, this study demonstrated no clear significant benefit for *pain affect* and other pain subdomains when using CBM compared to placebo. Key limitations included the small sample size, short duration of intervention follow-up and no inclusion of RDEB participants, which limits generalizability.

Nevertheless, several strengths pertain to the rigorous study methodology and confirmed feasibility of short-term tolerability of sublingual CBMs, coupled with reduced concomitant analgesic use, aligning with prior observational data [4,6]. These suggest potential avenues for future research, including larger, longer duration, multicentre trials targeting specific EB subtypes and optimized CBM formulations to better elucidate their therapeutic potential in EB.

ACKNOWLEDGMENTS:

We are deeply grateful to the patients with EB and their families for their active participation prior to and during the study. We thank the patient organization DEBRA-UK for their generous financial support, which funded participant recruitment and study materials. We also thank Felix Farma for providing the study drug, with the aim of helping marginal populations; Felix Farma and DEBRA-UK were not involved in any part of the data analysis. Finally, we acknowledge the valuable contributions of our partners in the epidermolysis bullosa research field, including clinical and methodological expertise that facilitated study design and execution.

Table 1: Participants are labelled A–H. Demographics and Baseline Surveys: Established cut-offs (DN-4: >3; CSI: male >24, female >32; HADS: possible disorder 8–10, likely disorder 11–21; PCS: >30; PSEQ: <40). Abbreviations: NRS, numeric rating scale; DN-4, doleur neuropathique 4 questions; CSI, central sensitization inventory; PSEQ, pain self-efficacy questionnaire; SF-MPQ2, short-form McGill pain questionnaire version 2; HADS, hospital anxiety and depression scale; PCS, pain catastrophizing scale.

	Participant A-H		A	B	C	D	E	F	G	H	Group A-H median (IQR) [25th–75th percentiles]
Demographics	Age		31	63	32	28	75	24	16	21	29.5 (16.5) [23.25–39.75]
	Sex		F	M	F	F	F	M	F	M	
	EB-type		Simplex	Junctional	Dominant Dystrophic	Simplex	Junctional	Simplex	Simplex	Junctional	
	Previous CBM-use		No	Regular	No	No	Regular	No	No	Sporadic	
	Pain score at inclusion (NRS 0-10)		5	4	5	4	5	6	4	5	5.0 (1.0) [4.0–5.0]
	DN-4 (0-7)		3	5	4	5	4	3	3	4	4.0 (1.25) [3.0–4.25]
	CSI (0-100)		46	28	37	28	34	35	19	24	31.0 (8.5) [27.0–35.5]
Baseline Surveys	HADS	Total (0-42)	22	7	15	11	16	7	9	8	10.0 (7.5) [7.75–15.25]
		Anxiety (0-21)	7	5	8	7	9	6	6	5	6.5 (1.5) [5.75–7.25]
		Depression (0-21)	15	2	7	4	7	1	3	3	3.5 (4.25) [2.75–7.0]
	PCS (0-52)		33	18	9	14	9	16	8	10	12.0 (7.5) [9.0–16.5]

Table 1: (*continued*)

Baseline Surveys	Participant A-H		A	B	C	D	E	F	G	H	Group A-H median (IQR) [25th–75th percentiles]
	SF-MPQ2	Global	91	66	27	46	25	94	12	78	56.0 (54.75) [26.5–81.25]
		Affect (0-44)	20	20	5	2	0	8	0	10	6.5 (11.0) [1.5–12.5]
		Neuropathic (0-66)	26	4	8	16	8	21	6	20	12.0 (12.75) [7.5–20.25]
		Intermittent (0-66)	17	21	4	12	9	26	0	26	14.5 (14.5) [7.75–22.25]
		Continuous (0-66)	28	21	10	16	8	39	6	22	18.5 (14.0) [9.5–23.5]
	PSEQ	Global (0-60)	15	39	48	49	46	34	44	43	43.5 (8.75) [37.75–46.5]
	Pain Medication		-	-	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed); Oxycodon 5mg 1x daily	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed); Diclofenac 50mg 3x daily	

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Chapter

8

Full Report, unpublished

Sublingual Tetrahydrocannabinol and Cannabidiol to Treat Pain in Epidermolysis Bullosa: A Randomized, Placebo-Controlled Crossover Study

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Karin M. Vermeulen, Roy E. Stewart, José C. Duipmans and André P. Wolff

ABSTRACT

Background: Epidermolysis bullosa (EB) is a rare, inherited skin disorder causing severe fragility, blistering, and chronic pain, involving nociceptive, neuropathic, and nociplastic mechanisms. Conventional analgesics often fail, prompting exploration of cannabinoid-based medicines (CBMs) for pain relief.

Objectives: To assess the effect of a sublingual CBM (10% THC, 5% CBD) on pain affect in patients with EB.

Methods: A randomized, placebo-controlled, double-blind, crossover design was employed at the University Medical Centre Groningen, Netherlands. Eight adult EB patients (EBS, n=4; JEB, n=3; DDEB, n=1; median age 29.5 years) with baseline pain ≥4 (NRS) were enrolled. Participants received CBM or placebo for 2 weeks, a 2-week washout, then crossed over. The primary outcome was pain affect change (SF-MPQ-2). Secondary outcomes included other pain subscales, pain self-efficacy (PSEQ), analgesic use, and adverse events. Baseline surveys were utilized as descriptive proxies assessing neuropathic pain, central sensitization, pain catastrophizing, and anxiety/depression.

Results: The primary outcome, pain affect did not statistically significantly improve (CBM: -1.1, SD=5.1, p=0.69; placebo: -4.6, SD=8.8, p=1) nor in other pain subscales (p>0.05). Non-statistically significant trends toward improved outcomes were observed, including CBM achieving ≥30% global pain reduction in 75% of participants (6/8) versus 50% (4/8) for placebo. Analgesic use dropped 50% with CBM, not placebo. Adverse events (CBM: n=20; placebo: n=7), were mild (n=18) or moderate (n=9), and resolved quickly.

Conclusion: This trial found no significant improvement with CBM in the primary outcome, pain affect, likely due to small sample size. Reduced analgesic use and pain trends suggest potential benefits, warranting larger controlled trials.

INTRODUCTION

Epidermolysis bullosa (EB) is a group of rare, inherited skin disorders characterized by extreme fragility and blistering, which significantly impairs quality of life [22,25,55]. Pathological changes in EB can also manifest extracutaneously, leading to highly heterogeneous clinical presentations, severity, and disease progression. The four main types of EB are EB simplex (EBS), junctional EB (JEB), dystrophic EB (including recessive [RDEB] and dominant [DDEB] forms), and Kindler syndrome.

One of the most challenging aspects reported by patients is the management of pain [47,48]. Pain in EB arises from primary factors comprising blistering, wounds, scarring, and malignancies, as well as secondary factors involving infections, dressing changes, and medical procedures. Traditionally, EB-related pain has been attributed to nociceptive pathways due to mechanical and inflammatory stress on the skin and mucosa. However, conventional treatments based on nociceptive etiology, such as opioids, are often ineffective and result in tolerance and burdensome side effects [19]. The complex pain-presentation and management seen in EB might be explained by the fact that individuals with EB are likely to experience a mixed pain state, involving a combination of nociceptive, neuropathic, and nociplastic mechanisms [18,40].

In a recent cross-sectional study on pain descriptors, the most severe pain descriptor reported across all EB subtypes was an "unpleasant" type pain [48]. Pain descriptors provide clues as to the underlying etiology, and this descriptor has been linked to pain affect, the emotional processing and modulation of pain [8,42]. Pain affect has a close bidirectional relationship with nociplastic pain, which is defined as pain arising from lowered pain thresholds without demonstrable underlying somatic nociceptive or neuropathic pathology. Conversely, heightened emotional distress can further lower pain thresholds, perpetuating nociplastic pain and creating a vicious cycle that results in chronic pain. In EB, the combination of persistent skin fragility, dysregulation of the skin microenvironment including neuronal and inflammatory signaling, and recurrent trauma, seems to predispose patients to developing chronic mixed-pain [19]. Given that peripherally acting analgesics minimally modulate pain affect, a central process, this may clarify the constrained effectiveness of standard evidence-based pain-relief approaches in EB.

To date, several case reports and surveys have explored the use of cannabinoid-based medicines (CBMs) in EB, reporting, amongst others, improvements in pain outcomes [11,31,33,44,46,59]. In one study, half of RDEB patients registered to an expert centre used CBMs with similar reported improvements [28]. In other non-EB chronic pain conditions the effects of cannabinoids, namely, tetrahydrocannabinol (THC) and cannabidiol (CBD), have been shown to modulate neurotransmitter activity, especially in areas potentiating pain affect [5,58]. Several studies, as demonstrated in a recent meta-analysis however, observed only limited efficacy for a range of chronic pain conditions [61]. Whether CBMs modulate pain affect, and general pain perception in EB has yet to be studied.

Given the unmet need for effective pain treatment in EB, higher-quality clinical investigations into the therapeutic role of CBMs in EB are warranted, with the intention to optimize pain management, and improve patient outcomes. This exploratory controlled trial aimed to address this gap by assessing the effectiveness of a sublingually administered CBM on pain affect in patients with EB, utilizing a pharmaceutically standardized cannabinoid composition.

METHODS

Study design and setting

This single-centre clinical study utilized a randomized, placebo-controlled, double-blind, cross-over design in adult patients with EB living in the Netherlands. Participants were recruited from the Centre for Blistering Diseases at the University Medical Centre of Groningen (UMCG), a member of the European Reference Network for EB. Patient involvement included presentation of the study design at a research oriented symposium for patients and an online presentation and discussion of the study methodology. Patient-derived feedback was assessed and necessary methodology changes were incorporated by the research team. A data safety monitoring board consisting of 3 independent experts reviewed blinded study data and interim outcomes at halfway, and at study closure. The study was completed in accordance with the declaration of Helsinki (good clinical practice guidelines) and was approved by the Medical Ethical Committee of the UMCG (*Sponsor protocol number: 202000638 / EudraCT number: 2021-000103-20*).

Study participants

Eligible patients were informed about the study and invited to participate by telephone, video calling, or during regular out-patient visits. Patients were included if they had a genetic diagnosis of congenital EB; were at least 16 years old at study onset; could read and write in Dutch; were legally capable of providing informed consent; and reported an average pain score of ≥4 on a numeric rating scale (NRS) (0–10) over the past week.

Ineligibility pertained to participation in conflicting clinical trials, recent (≤12 months) myocardial infarction or significant cardiac dysfunction, known psychotic disorders or history of suicidal ideation, or had a history of substance addiction requiring hospitalization. Female and male participants of childbearing potential were informed about contraceptive precautions. Patients were also ineligible if they had used cannabis or cannabinoid-based medications within 30 days prior to study enrolment and were unwilling to abstain, or if they had significant renal or hepatic impairment.

For this crossover study, the sample size was calculated to achieve 80% statistical power with an alpha level of 0.05, targeting a 30% improvement in the primary outcome. The required sample size was determined to be n=9 participants [45].

Study Interventions

The study intervention was a cannabinoid-based medicine oil (CBM) containing 100 mg/mL THC and 50 mg/mL CBD, equivalent to 10% THC and 5% CBD. The pharmaceutical-grade cannabis *flos* is produced by Bedrocan B.V. (Utrecht, The Netherlands) and processed by Felix Farma (The Hague, The Netherlands), where cannabinoids were extracted using an ethanol-based method. The resulting CBM has a standardized cannabinoid composition within regulatory limits and is administered sublingually via a one-millilitre syringe. The placebo underwent the same production process, with THC and CBD removed, ensuring similar texture, colour, and taste.

Participants followed care as usual, continuing pain treatments according to their current prescriptions and EB breakthrough pain guidelines [19]. All participant reported, and researcher reported outcomes were recorded within the research electronic data capture system (REDCap).

Participants were randomized into two groups using *www.randomizer.org,* with the allocation process managed by the research pharmacy. The randomization list, accessible exclusively to the research pharmacists, was available to the Principal Investigator upon request 24/7 throughout the study duration. Group 1 received CBM followed by placebo, while Group 2 received placebo followed by CBM. The study period consisted of 7 weeks subdivided into 4 parts: a) 1 week baseline, b) 2 weeks intervention A, c) 2 weeks washout, d) 2 weeks intervention B. Unblinded data was only requested after all statistical analyses were completed.

The detailed methodology of this study has been previously described in an earlier publication [45].

Outcomes

The primary outcome was assessed using numeric rating scale (NRS, min-max 0-10) scores from the Short-form McGill Pain Questionnaire 2 (SF-MPQ-2) [14]. This was measured as the difference in mean scores pre- (baseline) and post-intervention (CBM and placebo) for each group using the subscale items pertaining to "pain affect".

Secondary outcomes included other subscales from the SF-MPQ-2 (continuous, intermittent, neuropathic and global score) [15]. Additionally, the Pain Self-Efficacy Questionnaire (PSEQ) was analyzed longitudinally. The PSEQ measures an individual's confidence in performing activities despite experiencing chronic pain [38]. For the SF-MPQ-2 and PSEQ NRS improvements by ≥30% were considered clinically meaningful [16]. Minimal clinically important difference (MCID) scores have not been determined for pain interventions in EB. Other outcomes included the concomitant use of, and change in analgesic medication and titration dose-achieved of CBM and placebo. Adverse events were recorded following CTCAE classification [36].

Four baseline surveys described the study population: (1) Pain Catastrophizing Scale (PCS). The PCS assesses pain catastrophizing, including rumination, magnification, and helplessness [13,54]. (2) Douleur Neuropathique 4 (DN4). The DN4 assesses neuropathic pain qualities and screens for neuropathic pain through sensory symptoms. The 7-item DN4 using only participant reported pain qualities was administered (the cutoff score of 4 has a sensitivity and specificity of 74% and 79%) [50]. (3) Central Sensitization Inventory (CSI). The CSI assesses central sensitization symptoms, including physical and emotional symptoms (cutoff scores,

sensitivity, and specificity of 30, 85%, and 93% (overall), 33, 83%, and 97% (female), and 25, 89%, and 91% (male)) [32,49]. (4) Hospital Anxiety and Depression Scale (HADS). This scale measures anxiety and depression using these subscales to detect emotional distress without physical symptom interference (the established cutoff score, sensitivity and specificity are 8, 82% and 78%) [52,60].

Statistical Analysis

Baseline surveys were collected and summarized descriptively in the results. Distributions of the SF-MPQ and PSEQ survey data were visually inspected (histograms and box plots). Due to the skewed nature of the outcome data and non-symmetry, differences were assessed using the sign test between baseline and CBM or placebo, for the outcome variables. For ease of interpretation we present means for longitudinal outcomes and medians for single-administered questionnaires.

Functional Magnetic Resonance Imaging (fMRI)

Of eight C4EB participants, three met fMRI safety criteria; five were excluded due to ferromagnetic wound-care materials or other contraindications. Participants: A (EB simplex [EBS], female, 31 years, CBM-naïve), E (junctional EB [JEB], female, 75 years, regular prior CBM user), and G (EBS, female, 16 years, CBM-naïve). Resting state functional magnetic resonance imaging (rs-fMRI) was acquired at three timepoints (baseline; penultimate day of each two-week intervention period) using a 3T Siemens MAGNETOM Prisma scanner (Cognitive Neuroscience Center, UMCG). Data were preprocessed with fMRIPrep 24.1.1 [17] and post-processed with XCP-D 0.10.1 [34]. Pearson correlations between BOLD time-series from pain-relevant regions (anterior and posterior insula, thalamus, amygdala, parietal cortex, and ACC) and between seven canonical resting-state networks were computed per participant [56], comparing CBM versus placebo periods. Magnitudes ≥ 0.4 or ≤ -0.4 were considered clinically meaningful. Full correlation matrices are provided as supplementary material. Ethical approval as stated in the Study design and setting section.

Eighty-three patients were contacted by the study centre (UMCG), these were patients deemed eligible by the head nurse practitioner as they were known to experience pain because of their EB, and had been in touch with the EB clinic within the past year. Of the 83 patients, 74 refused participation or did not meet the inclusion criteria, reasons given are listed in figure 1. Nine patients were included for participation, subsequently 1 participant withdrew due to a protocol violation and was excluded before analysis.

Table 1: Participants are labelled A–H. Demographics and Baseline Surveys: Established cut-offs (DN-4: >3; CSI: male >24, female >32; HADS: possible disorder 8–10, likely disorder 11–21; PCS: >30; PSEQ: <40). Abbreviations: NRS, numeric rating scale; DN-4, doleur neuropathique 4 questions; CSI, central sensitization inventory; PSEQ, pain self-efficacy questionnaire; SF-MPQ2, short-form McGill pain questionnaire version 2; HADS, hospital anxiety and depression scale; PCS, pain catastrophizing scale

	Participant A-H		A	B	C	D	E	F	G	H	Group A-H median (IQR) [25th–75th percentiles]
Demographics	Age		31	63	32	28	75	24	16	21	29.5 (16.5) [23.25–39.75]
	Sex		F	M	F	F	F	M	F	M	
	EB-type		Simplex	Junctional	Dominant Dystrophic	Simplex	Junctional	Simplex	Simplex	Junctional	
	Previous CBM-use		No	Regular	No	No	Regular	No	No	Sporadic	
	Pain score at inclusion (NRS 0-10)		5	4	5	4	5	6	4	5	5.0 (1.0) [4.0–5.0]
	DN-4 (0-7)		3	5	4	5	4	3	3	4	4.0 (1.25) [3.0–4.25]
Baseline Surveys	CSI (0-100)		46	28	37	28	34	35	19	24	31.0 (8.5) [27.0–35.5]
	HADS	Total (0-42)	22	7	15	11	16	7	9	8	10.0 (7.5) [7.75–15.25]
		Anxiety (0-21)	7	5	8	7	9	6	6	5	6.5 (1.5) [5.75–7.25]
		Depression (0-21)	15	2	7	4	7	1	3	3	3.5 (4.25) [2.75–7.0]
	PCS (0-52)		33	18	9	14	9	16	8	10	12.0 (7.5) [9.0–16.5]

Table 1: Table 1: Demographics and Baseline Surveys (*continued*)

	Participant A-H		A	B	C	D	E	F	G	H	Group A-H median (IQR) [25th–75th percentiles]
Baseline Surveys	SF-MPQ2	Global	91	66	27	46	25	94	12	78	56.0 (54.75) [26.5–81.25]
		Affect (0–44)	20	20	5	2	0	8	0	10	6.5 (11.0) [1.5–12.5]
		Neuropathic (0–66)	26	4	8	16	8	21	6	20	12.0 (12.75) [7.5–20.25]
		Intermittent (0–66)	17	21	4	12	9	26	0	26	14.5 (14.5) [7.75–22.25]
		Continuous (0–66)	28	21	10	16	8	39	6	22	18.5 (14.0) [9.5–23.5]
	PSEQ	Global (0–60)	15	39	48	49	46	34	44	43	43.5 (8.75) [37.75–46.5]
	Pain Medication		-	-	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed); Oxycodon 5mg 1x daily	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed)	Acetaminophen 1000mg 4x daily (when needed); Diclofenac 50mg 3x daily	

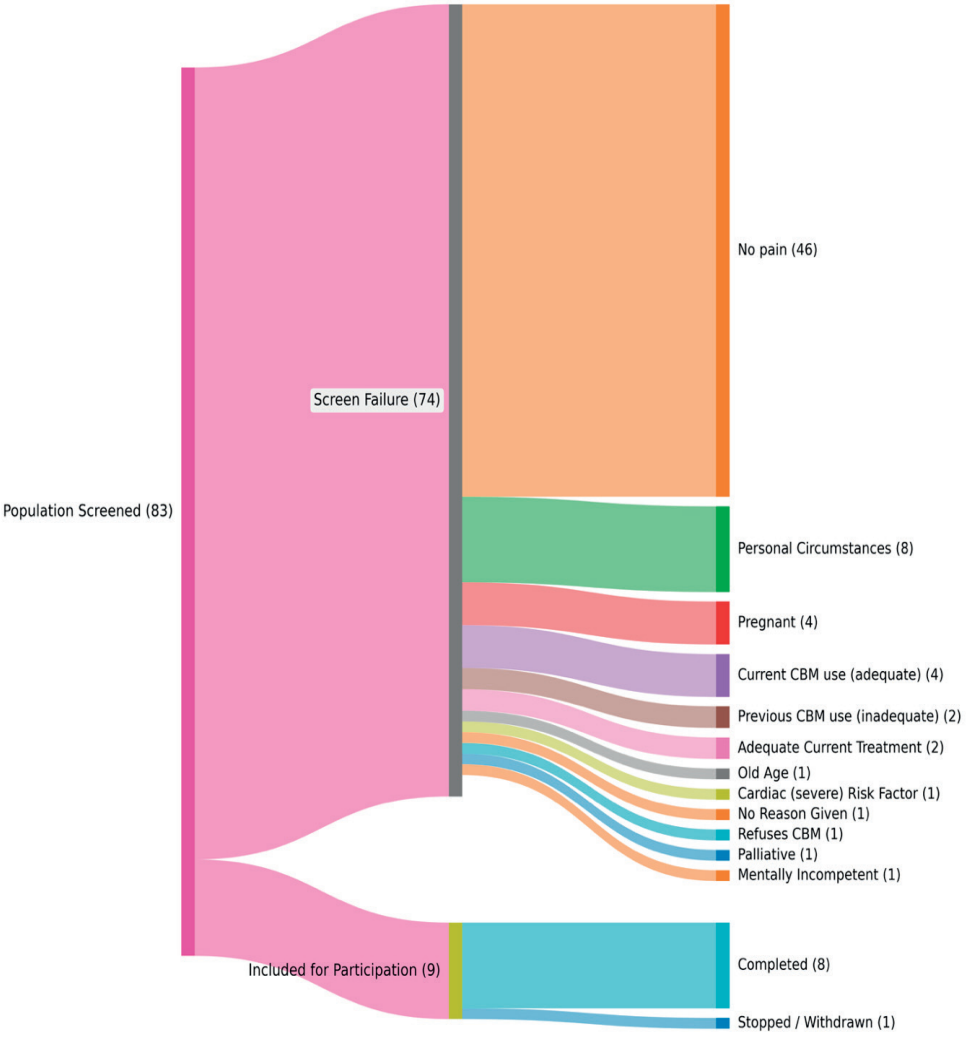


Figure 1: Flow Diagram of Participant Inclusion and Exclusion or Screen Failure.

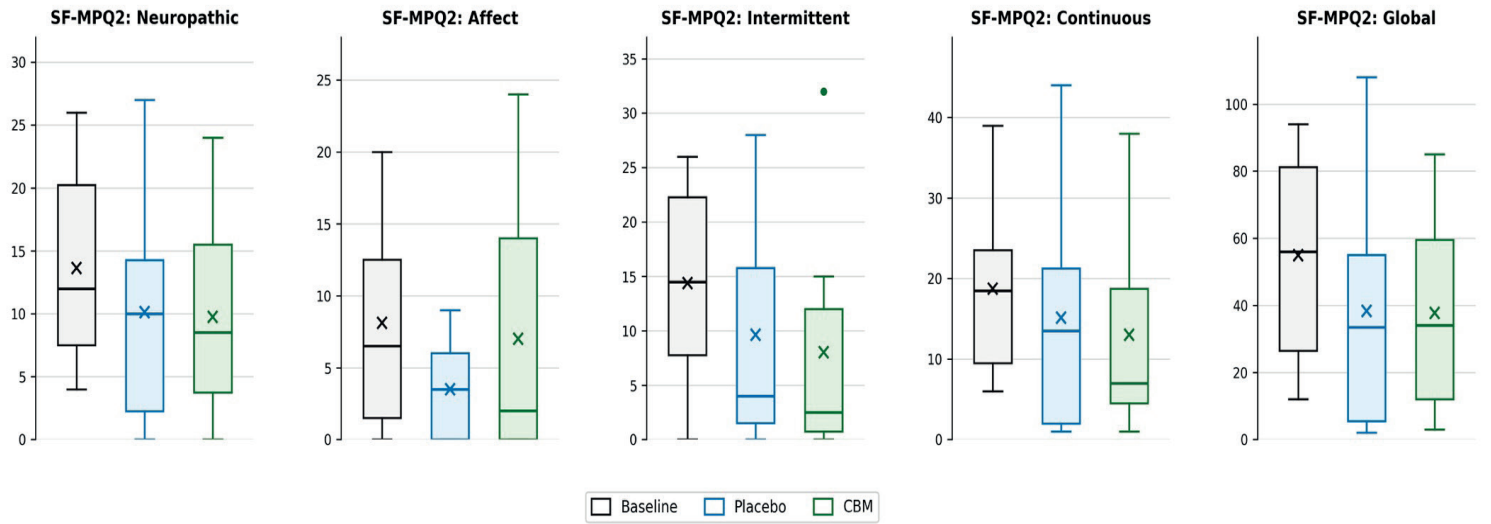


Figure 2: (a–e) Box plots of SF-MPQ-2 pain scores for baseline, placebo, and CBM interventions in n=8. Boxes represent the interquartile range (IQR, calculated using the inclusive method), with the median shown as the central line. Whiskers extend to the minimum and maximum values. Outliers, if present, are plotted as individual point

RESULTS

A total of nine participants were randomized to receive the interventions within a 12 month period. After baseline measurements, one participant was excluded from ongoing participation due to a protocol violation (*Figure 1*). The resulting population consisted of eight participants (n=5 females, n=3 males), evenly randomized into two groups: CBM-Placebo (n=4) and Placebo-CBM (n=4) (*Table 1*). Participants represented three EB subtypes: EBS (n=4), JEB (n=3), and DDEB (n=1), with a median age of 29.5 years (IQR=16.5).

Baseline Surveys

The median global SF-MPQ-2 score was 56 (IQR=54.8), derived from four subscales: continuous pain (19, IQR=9.3), intermittent pain (15, IQR=4.3), neuropathic pain (12, IQR=8), and pain affect (7, IQR=12.5). The median 7-item DN4 score was 4 (IQR=1.3), with 5 out of 8 participants (63%) meeting the cutoff score for possible neuropathic pain. The median CSI score for this population was 31 (IQR=8.5). Three out of five (60%) females and two out of three (67%) males scored above the cut-off for possible central sensitization disorder.

Median PSEQ score was 43.5 (IQR=8.8), with half of the participants (n=4) scoring below the cutoff, indicating lower levels of pain self-efficacy. The median global HADS score was 10 (IQR=4.9), with subscale medians of 6.5 (IQR=1.5) for anxiety and 3.5 (IQR=2.9) for depression, both below the clinical cutoff of 11 for probable anxiety or depressive disorder. Scores at or above this cutoff on either subscale suggest possible anxiety (n=1) or depression (n=1), indicating further clinical investigation rather than a definitive diagnosis. The median PCS score in this population was 12 (IQR=6), with only one participant scoring above the cutoff for clinically significant pain catastrophizing.

There were no statistically significant differences in number of researcher-participant contact moments between CBM and placebo interventions.

Dose-achieved: sub-side effect threshold dose

Participants were instructed to escalate their dose according to a titration scheme, adjusting based on the onset of side effects by reducing their dose to the level of the previous day in the scheme [45]. For CBM, the median titration dose was reached in 7 days (IQR=10), equivalent to 30mg THC and 15mg CBD daily, compared to 14 days (IQR=0) for placebo

(*Table S2*). Intraindividual variability was assessed using the coefficient of variation (CV), yielding high variability for CBM (62%) in contrast to placebo (0%) (*Table S2*).

Medication-use

Within the study population, six participants reported using medication for pain at screening, with a total of 8 medications documented. *Acetaminophen* was the most frequently used pain medication, reported by six participants (75%). Other analgesics included *oxycodone* (n=1) and diclofenac (n=1). During the CBM intervention, half of all pain medications, including oxycodone, were discontinued (n=4, 50%). During placebo intervention all analgesics were used as was reported during baseline (*Table S1*).

Primary Outcome: Pain Affect

The mean change scores in the pain affect subscale of the SF-MPQ2 were evaluated (total item score range was 0-44) (*Figure 2*). For the CBM group, the mean change was -1.1 (SD=5.1, p=0.69), whereas the placebo group exhibited a mean change of -4.6 (SD=8.8, p=1). No statistically significant differences were detected in either group (p>0.05), indicating that neither intervention significantly modified pain affect relative to baseline on a group level. A ≥30% reduction of pain affect was achieved by 3/8 (38%) participants in both CBM and placebo groups.

Other Pain Outcomes

During CBM intervention 6/8 (75%) of participants achieved global SF-MPQ2 pain reduction ≥30%, compared to 4/8 (50%) during placebo (*Table S3)* but this difference was not statistically significant.

Differences across other pain subscales were also examined. For *continuous pain*, mean changes were -5.8 (SD=10.4, p=0.07) for CBM and -3.6 (SD=3.6, p=1) for placebo. For *intermittent* pain, mean changes were -6.4 (SD=7.5, p=0.29) for CBM and -4.8 (SD=8.5, p=1) for placebo. For *neuropathic* pain, mean changes were -3.9 (SD=2.7, p=0.07) for CBM and -3.5 (SD=6.9, p=0.29) for placebo. These results show no statistically significant reduction in any pain subscales between baseline and CBM or placebo. A ≥30% reduction of pain in these subscales were achieved by participants as follows: *affect* (CBM: n=3, placebo n=3), *continuous* (CBM: n=6, placebo: n=4), *intermittent* (CBM: n=6 , placebo: n=3) and *neuropathic* (CBM: n=3, placebo: n=4).

Seven of eight participants (88%) reported greater pain improvement (SF-MPQ2 global score) during the first administered intervention, than the second, independent of whether administering CBM or placebo.

No statistically significant differences in pain self-efficacy, as measured by the PSEQ, were observed for CBM (p=0.35) or placebo (p=0.50), indicating that neither intervention affected pain self-efficacy. No participants achieved PSEQ improvements of ≥30%.

Adverse Events

A total of 27 adverse events (AE) were recorded (CBM: n=20, placebo: n=7) (*Table S4*). The AE incidence rates for CBM and placebo were 2.5 and 1.3 AEs per participant per week, respectively. *Dizziness* was the most frequent (n=6; CBM: n=5, placebo: n=1), followed by *dry mouth* and *euphoria* (n=3, each). Most AEs resolved within 1 day (n=20), while 5 lasted 1–2 days and 2 (CBM group only) persisted for 2–3 days. AEs were predominantly *probably*- (n=13) or *possibly*- (n=11) related to the study drug, with 20 AEs (74%) classified as *expected.* AE severity was predominantly *mild* (n=18) or *moderate* (n=9), with no *severe*. Management involved *watchful waiting* (n=12) *dose reduction* (n=8), *dose-holding* (n=4), or *temporary discontinuation* (n=3). All AEs resolved without prolonged or permanent sequelae.

fMRI

Connectivity findings are summarised in Table D. Participant A (CBM-naïve, age 31) showed reduced right–left amygdala connectivity (r = −0.53) and reduced left posterior insula–ACC connectivity (r = −0.42). Network-level analysis revealed increased limbic–somatomotor coupling (r = +0.43) and decreased frontoparietal–ventral attention connectivity (r = −0.46), suggesting heightened sensory-emotional integration alongside reallocation of pain-directed attention.

Participant E (regular prior CBM user, age 75) showed minimal pain-circuit reorganisation. Increased left thalamus–ACC connectivity (r = +0.54) and increased frontoparietal–dorsal attention coupling (r = +0.40) may reflect neuroplastic adaptation from chronic prior CBM exposure.

Participant G (CBM-naïve, age 16) showed increased right posterior insula–ACC (r = +0.46) and insula–parietal (r = +0.50) connectivity, alongside reduced limbic–ventral attention (r = −0.41) and default mode

network (DMN)–frontoparietal (r = -0.49) coupling, consistent with reduced emotional hypervigilance to pain.

DISCUSSION

This randomized, placebo-controlled crossover study primarily aimed to evaluate the effectiveness of CBM in modulating pain affect in EB. Our hypothesis pertained specifically to the effectiveness of a standardized CBM comprising THC (10%) and CBD (5%), administered over two weeks. The results show that CBM did not demonstrate significant differences on pain affect, compared to placebo, as assessed by the SF-MPQ2. Nor were any significant differences observed in the SF-MPQ2 global score or its other pain subscales. An exploratory rs-fMRI sub-study was additionally conducted in three eligible participants to examine central cannabinoid effects on pain-related brain connectivity; these findings are discussed below. Despite these outcomes, CBM intervention was well tolerated and demonstrated beneficial trends in reduced concomitant analgesic use and more participants (n=6) achieving a clinically meaningful global pain reduction ≥30% compared to placebo (n=4).

The notable trend toward reduced analgesic requirements, including oxycodone, was observed during the CBM intervention only. Several studies have indicated that co-administration of CBMs aids tapering of other analgesics, including opioids [1,12,30,39]. It is important to consider the increased drug and administration burden when incorporating CBMs into a pain treatment regimen, as demonstrated in a recent study on chronic pain where combining intrapulmonary CBM with oxycodone provided no advantage over either treatment alone, except for a reduction in opioid tablet intake, albeit with a higher overall drug burden [12]. Despite minimal analgesic use, pain scores at inclusion were high, which is consistent with other reports suggesting that current treatments are inadequate or not well tolerated in EB [6,24]. Over half participants scored above the CSI cutoff, suggesting possible central sensitization in the majority of the study population, again, adding a layer of complexity to their pain management, and underpinning the limited role here for peripherally acting analgesics. A formal assessment using quantitative sensory testing (QST) is required to assess altered somatosensory function due to central sensitization, which should be considered in future studies [43].

It is well known in EB that pain levels negatively correlate with the ability to perform daily tasks [26,47]. Interestingly only three participants showed considerably low self-efficacy at baseline, however changes could not be clearly attributed to either CBM or placebo, aligning with the overall absence of significant effects observed across all pain outcomes in this study.

These findings follow a trend of mixed-results in CBM-related clinical trials on various (chronic) pain conditions. Summative reviews suggest at most, moderate analgesia with limited effect sizes, and may be a consequence of a lack of standardization across studies for CBM composition, quality and dosing [3,29,61]. A systematic review of qualitative studies reported that patients' perceptions of pain relief with CBM treatment often do not align with research findings [37]. This could be a similar case in EB as our clinical study did not confirm the previously reported patient and clinician experiences [11,31,44,46,59]. It remains unclear which factors contribute to this discrepancy. A prior survey study and a recent review both suggest that the perceived benefits of CBMs likely stem from cumulative effects of multiple favourable outcomes, such as sleep quality, increased mobility, improved mood, and reduced dependence on concomitant medications, and may go undetected when solely assessing conventional pain outcomes [35,46].

Notably, seven of eight participants reported more pain improvement (SF-MPQ2 global score) during the first intervention, irrespective of receiving CBM or placebo. This observation suggests a pronounced influence of placebo effects and expectation bias, likely driven by heightened optimism and motivation at the study's outset, and may be a pitfall of the crossover design [10,23]. The sole exception here, participant C (EB-type: DDEB, sex: F, age: 32), who did not follow this trend, exhibited marked improvements across all pain subscales, including a global pain improvement of 44% during the second phase with CBM compared to placebo in the first phase (33% worsening). Interestingly, this participant was the only individual diagnosed with DDEB, potentially suggesting subtype-specific responsiveness to CBM. Unfortunately, no RDEB participants were included in this trial, despite this subgroup comprising over 50% of respondents in a recent cross-sectional study on CBM use in EB [46].

For this study, we chose an oromucosal route of administration based on prior experience at our center, incorporating patient feedback from clini-

cal practice. The scientific literature further supports this choice, emphasizing ease of use, feasible stepwise titration, and adequate bioavailability [7,53]. This study observed a highly tolerable adverse event profile, with no participant withdrawals due to adverse events, in contrast to a recent study by the same manufacturer in the Netherlands, where 31% of participants receiving intrapulmonary CBMs withdrew within the first 2–3 weeks [12]. In our study, the typical adverse event lasted less than 1 day, was mild, and resolved with watchful waiting. No participants necessitated additional medical intervention, and adverse events disappeared spontaneously, or could be adequately managed through dose reduction, following the titration protocol meeting the sub-side effect threshold maintenance dose. Future investigations could further minimize side effect burden by elucidating the potential of alternative administration forms, such as topical administration, or CBM compositions without psychotropic cannabinoids [41].

Furthermore, we hypothesized that the dose achieved with placebo would exceed that of CBM, as titration depended on the onset and tolerance of expected side effects. Notably, in all cases, placebo was titrated to the maximum dose despite seven reported adverse events, whereas only three participants reached this maximum dose during CBM titration (two of these participants reported self-limiting and quickly resolving *dizziness* and *nausea,* however continued titration in the absence of adverse event recurrence). Additionally, high levels of interindividual variability in CBM dosing was observed, likely attributable to factors such as age, sex, prior cannabinoid exposure, genetic profiles, and the underlying tone of the human endocannabinoid system [2,57].

Finally, for the first time the safety and feasibility of rs-fMRI was demonstrated within an EB clinical trial, providing hypothesis-generating insights into central cannabinoid effects on pain-related brain connectivity. With only three eligible participants, group-level inference is not possible; the divergent connectivity patterns likely reflect differences in prior CBM exposure, EB subtype, and baseline sensitisation state, as well as inter and intra individual variability between participants and timepoints inherent to rs-fMRI techniques. Five of eight participants were ineligible for fMRI, primarily due to metalic implants, or unwillingness to participate due to a high perceived burden. Future controlled CBM trials in EB could incorporate rs-fMRI as a pre-specified endpoint in larger cohorts to enable adequately powered, sub-studies.

Study limitations

As we expected, the study population had considerable heterogeneity in demographic and disease-related factors, whereby several limitations warrant consideration.

Primarily, the small sample size restricted the study's methodological power. Even though this is the case, this study recruited the largest sample for a single clinical trial for EB in the Netherlands, to date. Of the 83 patients successfully contacted from our centre, unfortunately, most were ineligible or declined participation, as outlined in Figure 1, returning an enrollment ratio of 9:1. Importantly, 6 patients refused participation because they did not want to deviate from their current (effective) pain treatment; four were already using CBMs. In EB, achieving adequate symptom relief is often challenging, and it is understandable that patients may feel reluctant to modify effective therapeutic regimens. Encouragingly, the study showed a high retention rate (8/9, 89%) and revealed that half of the patients pre-selected to be contacted for study recruitment, for whom pain was an expected phenotype, were not experiencing pain at the time of inclusion.

Another challenge was the potential bias caused by disease heterogeneity. EB exhibits considerable symptom variation both between and within subtypes, that can fluctuate weekly due to disease activity, injury, infections, and psychosocial factors [21,51]. The study design attempted to limit intervention exposure to two periods of two weeks, in order to both minimize participation burden as well as precede fluctuations in disease activity. However two participants clearly showed considerable pain worsening during placebo intervention when compared to baseline even when continuing pre-existing analgesic regimens. Performing additional baseline outcome measurements in future studies, prior to each intervention, or implementing longer intervention exposure may improve the reliability of the longitudinal pain scores.

The participant-reported outcome questionnaires employed in this study may not have fully captured the individual benefits derived from the interventions. While we focused primarily on pain affect and included several additional outcomes, there is no current consensus on relevant outcome tools in EB. Recent studies underscore the need for validated core outcome sets in EB studies to facilitate comparisons across different clinical studies reliably [27]. Moreover, incorporating patient benefit index surveys—where outcome scores are weighted based on the im-

portance each participant assigns to specific outcomes—could provide more robust, real-world data and better highlight responses or efficacies tailored to individual participants [47]. Utilizing such a tool appears more relevant when effectiveness is expected on multiple domains (e.g. pain, sleep, wounds, anxiety), such as with CBMs.

Lastly, to address the pressing need for adequate pain alleviation in EB, it should be noted that there are important benefits to researching treatments targeted at specific patho-mechanisms of pain within the mixed-pain type we hypothesize in EB. A recent example of this in practice was a study that delineated small fiber neuropathies in RDEB, leading to promising trial results using pregabalin [4,9].

CONCLUSION

To the best of our knowledge, this is the first randomized controlled trial investigating CBM effectiveness for pain in EB, and is the second study to date where pain comprises the primary outcome in an EB-related clinical trial [9,45]. Despite growing patient and clinician reported benefits of CBMs in EB, this study demonstrated no clear benefits on the use of CBM on pain affect or other subdomains when compared to placebo, however, the small sample size limits generalisability to the broader EB patient population. Nevertheless, adequate drug tolerability and reduced concomitant analgesic use suggest potential avenues for future research, including larger, longer duration, multicenter trials targeting specific EB subtypes and optimized CBM formulations to better elucidate their therapeutic potential in EB.

ACKNOWLEDGEMENTS

We are deeply grateful to the patients with epidermolysis bullosa and their families for their active participation prior to and during the study. We thank the patient organization DEBRA-UK for their generous financial support, which funded participant recruitment and study materials. We also thank Felix Farma for providing the study drug, with the aim of helping marginal populations; Felix Farma and DEBRA-UK were not involved in any part of the data analysis. Finally, we acknowledge the valuable contributions of our partners in the epidermolysis bullosa research field, including clinical and methodological expertise that facilitated study design and execution.

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APPENDIX

Table A: Titration day achieved per participant, including daily dose of THC & CBD in mg.

Participant ID	Titration day, CBM-oil	Dose daily THC (mg)	Dose daily CBD (mg)	Titration day, Placebo	Dose daily THC (mg)	Dose daily CBD (mg)
A	4	15	7.5	14	75	37.5
B	14	75	37.5	14	75	37.5
C	14	75	37.5	14	75	37.5
D	4	15	7.5	14	75	37.5
E	6	25	12.5	14	75	37.5
F	14	75	37.5	14	75	37.5
G	8	35	17.5	14	75	37.5
H	2	5	2.5	14	75	37.5
Mean	8.3	40.0	20.0	14.0	75.0	37.5
Standard Deviation	5.1	30.2	15.1	0.0	0.0	0.0
Min value	2			14		
Max value	14			14		
Coefficient of Variation (CV) – titration day achieved:	**CBM-oil:** 61.38% There is a high degree of variability in the titration days among participants.					
	Placebo: 0% No interindividual variability					

Table B. Participant and Researcher-Reported Outcomes — Participants A–D (continued on next page)

Participant		A	B	C	D
Age / Sex / EB-type		31 / F / Simplex	63 / M / Junctional	32 / F / Dom. Dystr.	28 / F / Simplex
DEMOGRAPHIC					
Previous CBM-use		No	Regular	No	No
Pain at inclusion (NRS 0–10)		5	4	5	4
BASELINE SURVEYS					
DN-4 (0–7)		3	5	4	5
CSI (0–100)		46	28	37	28
HADS	Total (0–42)	22	7	15	11
	Anxiety (0–21)	7	5	8	7
	Depression (0–21)	15	2	7	4
PCS (0–52)		33	18	9	14
INTERVENTION OUTCOMES					
fMRI performed		Yes	No	No	No
Toxicology (THC-COOH µg/L)	*CBM*	–	–	16	–
	Placebo	–	–	<5	–
Titration day achieved	*CBM*	4	14	14	4
	Placebo	14	14	14	14
PSEQ (% Δ from baseline)	*Baseline*	15	39	48	49
	CBM	15 (0)	37 (−5)	40 (−17)	48 (−2)
	Placebo	11 (−27)	35 (−10)	35 (−27)	51 (+4)
Global (0–242)	*Baseline*	91	66	27	46
	CBM	55 (−40)	46 (−30)	**15 (−44)**	22 (−52)
	Placebo	**31 (−66)**	**2 (−97)**	36 (+33)	**50 (+9)**
Affect	*Baseline*	20	20	5	2
	CBM	24 (+20)	14 (−30)	4 (−20)	0 (−100)
	Placebo	6 (−70)	0 (−100)	6 (+20)	5 (+150)
Neuropathic	*Baseline*	26	4	8	16
	CBM	24 (−8)	5 (+25)	5 (−38)	12 (−25)
	Placebo	9 (−65)	0 (−100)	11 (+38)	13 (−19)
Intermittent	*Baseline*	17	21	4	12
	CBM	0 (−100)	11 (−48)	1 (−75)	3 (−75)
	Placebo	3 (−82)	0 (−100)	5 (+25)	12 (0)
Continuous	*Baseline*	28	21	10	16
	CBM	7 (−75)	16 (−24)	5 (−50)	7 (−56)
	Placebo	13 (−54)	2 (−91)	14 (+40)	20 (+25)
Pain Medication	*Baseline*	–	–	Acetaminophen 1000mg prn	Acetaminophen 1000mg prn
	CBM	–	–	Stopped	Continued
	Placebo	–	–	Continued	Continued
Contact Moments	*CBM*	5	6	9	5
	Placebo	9	3	6	9

Legend: Exceeds cut-off Improved vs. baseline

Table B: Complete overview of Participant and Researcher-Reported Outcomes for Individual Participants enrolled in the C4EB Study. [Participants are labeled A–H. **Baseline Surveys:** Orange-highlighted cells indicate scores exceeding (worse than) established cut-offs (*DN-4: >3; CSI: male >24, female >32; HADS: possible disorder 8–10, likely disorder 11–21; PCS: >30; PSEQ: <40*). **Intervention Outcomes:** Green-highlighted cells show where the intervention (placebo and/or CBM oil) improved upon baseline scores. Global SF-MPQ-2 scores in **bold** reflect the intervention administered in Phase A. Certain SF-MPQ-2 subscale percentages are omitted when a percentage change could not be calculated due to a baseline score of 0.]

The median contact moments were 6 (IQR: 4–9) for CBM and 7 (IQR: 3–10) for placebo, with no significant difference between interventions (W=8.5, p>0.10).

Table B (continued). Participant and Researcher-Reported Outcomes — Participants E–H

Participant		E	F	G	H
Age / Sex / EB-type		75 / F / Junctional	24 / M / Simplex	16 / F / Simplex	21 / M / Junctional
DEMOGRAPHIC					
Previous CBM-use		Regular	No	No	Sporadic
Pain at inclusion (NRS 0–10)		5	6	4	5
BASELINE SURVEYS					
DN-4 (0–7)		4	3	3	4
CSI (0–100)		34	35	19	24
HADS	Total (0–42)	16	7	9	8
	Anxiety (0–21)	9	6	6	5
	Depression (0–21)	7	1	3	3
PCS (0–52)		9	16	8	10
INTERVENTION OUTCOMES					
fMRI performed		Yes	No	Yes	No
Toxicology (THC-COOH µg/L)	*CBM*	–	33	43	9
	Placebo	–	<5	<5	<5
Titration day achieved	*CBM*	6	14	8	2
	Placebo	14	14	14	14
PSEQ (% Δ from baseline)	*Baseline*	46	34	44	43
	CBM	18 (−61)	31 (−9)	49 (+11)	46 (+7)
	Placebo	30 (−35)	34 (0)	49 (+11)	49 (+14)
Global (0–242)	*Baseline*	25	94	12	78
	CBM	**3 (−88)**	**73 (−22)**	**3 (−75)**	85 (+9)
	Placebo	6 (−76)	108 (+15)	4 (−67)	**70 (−10)**
Affect	*Baseline*	0	8	0	10
	CBM	0 (0)	14 (+75)	0 (0)	0 (−100)
	Placebo	2 (–)	9 (+13)	0 (0)	0 (−100)
Neuropathic	*Baseline*	8	21	6	20
	CBM	0 (−100)	17 (−19)	0 (−100)	15 (−25)
	Placebo	0 (−100)	27 (+29)	3 (−50)	18 (−10)
Intermittent	*Baseline*	9	26	0	26
	CBM	0 (−100)	15 (−42)	2 (–)	32 (+23)
	Placebo	2 (−78)	28 (+8)	0 (0)	27 (+4)
Continuous	*Baseline*	8	39	6	22
	CBM	3 (−63)	27 (−31)	1 (−83)	38 (+73)
	Placebo	2 (−75)	44 (+13)	1 (−83)	25 (+14)
Pain Medication	*Baseline*	Oxycodone 5mg 1× daily; Acetaminophen 4× daily	Acetaminophen 1000mg prn	Acetaminophen 1000mg prn	Acetaminophen 1000mg prn; Diclofenac 50mg 3× daily
	CBM	Stopped	Continued	Continued	Acetaminophen stopped; Diclofenac continued
	Placebo	Continued	Continued	Continued	Continued
Contact Moments	*CBM*	8	4	6	6
	Placebo	3	10	9	3

Legend: Exceeds cut-off Improved vs. baseline

Table C: Adverse Events and Associated Characteristics.

Adverse Events and Outcomes		**Frequency, n**		
		Total	*CBM-oil*	*Placebo*
Adverse Event	Dizziness	6	5	1
	Insomnia	1	0	1
	Palpitations	2	2	0
	Anxiety	2	2	0
	Gastritis	2	1	1
	Flu like symptoms	1	0	1
	Nausea	2	1	1
	Dry mouth	3	2	1
	Euphoria	3	2	1
	Lethargy	2	2	0
	*Psychiatric disorders	1	1	0
	**Gastrointestinal disorders	1	1	0
	Dry eyes	1	1	0
	Total	27	20	7
Duration, days	<1	20	16	4
	1 - 2	5	2	3
	†2 - 3	2	2	0
Relationship to Drug	Possibly	11	7	4
	Probably	13	12	1
	Unlikely	2	0	2
	‡Not related	1	1	0
Expectedness	Expected	20	17	3
	Unexpected	7	3	4
Grade[a]	1 (Mild)	18	12	6
	2 (Moderate)	9	8	1
Action taken	Watchful waiting	12	9	3
	Drug dose reduced	8	7	1
	Drug dose held	4	1	3
	§Other	3	3	0
Outcome	Resolved	27	20	7

**disorientation (loss of sense of time)*, ***increased appetite*, †*dizziness*" ‡*flu-like symptoms* (n=1), 1x gastritis, §drug dose temporarily discontinued (own initiative participant, n=3). [a]AE's were reported using the CTCAE criteria version 5.0.[20]

Table D. Key resting-state fMRI connectivity changes during CBM vs. placebo periods.

Participant	Region pair	r
A (EBS, F, 31y, naïve)	R–L amygdala	−0.53
A	L post. insula – ACC	−0.42
A	Limbic–somatomotor (net)	+0.43
A	Frontoparietal–ventral att. (net)	−0.46
E (JEB, F, 75y, previous CBM user)	L thalamus – ACC	+0.54
E	Frontoparietal–dorsal att. (net)	+0.40
G (EBS, F, 16y, naïve)	R post. insula – ACC	+0.46
G	R post. insula – R parietal	+0.50
G	Limbic–ventral attention (net)	−0.41
G	DMN–frontoparietal (net)	−0.49

ACC, anterior cingulate cortex; att., attention network; CBM, cannabinoid-based medicine; DMN, default mode network; EBS, EB simplex; F, female; JEB, junctional EB; L, left; net, resting-state network; R, right. All correlation magnitutes <0.4 or <−0.4 are ommitted.

Chapter

9

General Discussion



SCOPE AND AIM

Epidermolysis bullosa (EB) is a rare inherited blistering skin disorder characterised by profound physical, psychological, and social burdens [9,15,21,34,37,64,103]. The defining clinical hallmarks, present from birth, are low-threshold blister formation and chronic wound development on the skin and mucous membranes. This thesis, however, demonstrates that consequences of EB extend substantially beyond the skin itself, whereby symptomatic burden is central.

Titled "Beyond the Blister", this thesis reflects a patient-driven shift in research focus, from the molecular and structural pathomechanisms of blister formation towards the symptomatic burden experienced by patients daily. The overall aim of this thesis was to investigate the therapeutic potential of cannabinoid-based medicines (CBMs) in the management of pain in EB.

Several studies were necessary to underscore the potential role of CBMs as relevant to patients living with EB and the clinicians managing them. **Part I** of this thesis (**Chapters 2-3**) explored symptomatic burdens, and **Part II** (**Chapters 4-8**) attempted to unravel evidence surrounding the use of CBMs in the management of EB.

Chapter 2 examined Dutch EB patient needs and perspectives on their current treatments, using the Patient Benefit Index (PBI) [88]. The significant impact and burden of pain became a clear unmet treatment need. These results led to **Chapter 3**, the subsequent characterisation of pain qualities across EB subtypes using the Pain Quality Assessment Scale (PQAS) [89]. This study demonstrated that pain scores were high across all EB subtypes, yet the pain quality *unpleasantness,* associated with affective pain processing, predominated when compared to nociceptive and neuropathic pain qualities.

Chapters 4 and 5 provided preliminary observational evidence on CBM-use and effects in EB through a case series and an international cross-sectional survey [84,87]. CBMs were both clinician- and patient-initiated and were regularly incorporated into symptomatic regimens in an international group of respondents. However, generalisability of these study results was limited by heterogeneous product-use, modes of administration and patient demographics. To formally address the missing link of methodologically rigorous clinical studies, **Chapter**

6 presented the design of the C4EB study, a randomised, double-blind, placebo-controlled crossover trial [85]. This was the first clinical trial investigating the effects of sublingual CBMs on pain in adults living with EB. Additionally, functional magnetic resonance imaging (fMRI) was implemented as a novel method of assessing pain as a clinical endpoint.

Chapters 7 and 8 reported the results of this trial [86]. The former presents the published findings of the C4EB study, reported as a research letter in the British Journal of Dermatology. The latter provides the complete, unpublished manuscript with full methodological detail and supplementary analyses.

The following chapter discusses the thesis findings in a broader context, addresses clinical implications, and outlines directions for future research.

PART I: PAIN IN EPIDERMOLYSIS BULLOSA

Patient-centred assessment as a prerequisite for meaningful research

Recommendation: Patient needs should drive the selection of outcomes in EB research, and instruments that capture individual, clinically meaningful change should be prioritised.

EB is considered an orphan disease, as clinical research is hampered by small patient populations, heterogeneous phenotypes, and a paucity of validated outcome instruments. Most outcome assessments applied historically in EB studies were adapted from tools developed for other dermatological conditions and were not designed to capture what matters most to EB patients. In fact, a striking 80 outcome domains for clinical studies in EB were identified between 1991 and 2021, demonstrating the challenge of pairing meaningful outcome measurements with the multiplicity of clinical features and consequences downstream from the blister [48]. A recent meta-analysis on pain-related intervention studies in EB also highlighted the significant heterogeneity in outcome tools implemented [80]. **Chapter 2** addressed this gap by applying the PBI to a Dutch EB patient cohort. Although not previously implemented in EB, the PBI is a validated instrument for general dermatologic conditions that explicitly incorporates patient-defined treatment needs and the degree to which those needs are perceived to be met by current care [2]. By including the patient's own weighting of outcomes, a PBI-styled assessment provides a clinically relevant and personalised representation of treatment benefit that conventional outcome assessments do not [1,2,8,44,52,114].

The findings of **Chapter 2** identified the four most important patient-determined treatment needs: to get better skin quickly, to be healed of all skin alterations, to be free of itching, and to be free of pain. Pain scores correlated positively with all 25 patient needs assessed in the questionnaire, underscoring the pervasive burden imposed by inadequately controlled pain across *every* domain of patient needs. This resonates with the international EB literature identifying this significant burden of pain across all EB demographic groups [10,22,25,32,39,60,82,89]. It also aligns with pain treatment mentioned in top research priorities for every EB type, consolidated in a recent international EB community workgroup [98]. Importantly, this finding justified the focus of subsequent chapters on pain as the primary therapeutic target.

Notably, self-reported disease severity correlated positively with nearly all patient needs, with the strongest association observed for the need to feel less depressed. This finding challenges a purely physical framing of EB disease burden: patients who perceive their disease as more severe do not necessarily carry a greater wound burden but appear to experience disproportionately greater psychological suffering. Disease severity in EB, as lived by patients, is therefore as much an emotional phenomenon as a physical one, and psychological consequences such as depression and pain affect, explored further in subsequent chapters, should be understood as intrinsic to the disease experience rather than incidental comorbidities.

More broadly, the use of patient-centred instruments in EB research represents a methodological advancement with implications beyond this thesis. In rare diseases, where traditional evidence hierarchies are often difficult to achieve, and heterogenous disease presentation is commonplace, capturing patient-defined outcomes may carry a significant weight in informing clinical decision-making and novel research avenues [28]. The findings of **Chapter 2** support a reorientation of EB clinical research towards outcomes that are meaningful at the level of the individual, a principle that directly informed the therapeutic questions explored in subsequent chapters.

Encouragingly, the patient-centred agenda discussed here is reflected at an international level through the Core Outcome Set for EB (COSEB) initiative [46,47]. Developed through a multi-stakeholder consensus process involving patient representatives, clinicians, researchers, and regulators across 24 countries, the initiative embeds patient involvement from its inception. The candidate domains under consideration, encompassing pain, pruritus, wound burden, and quality of life, closely mirror the unmet needs identified by EB patients in **Chapter 2**. The formation of COSEB and implementation of PBI-styled outcome assessments represent a necessary dual commitment in EB research: cross-study standardisation and patient-centred relevance.

Incorporating patient perspectives early on ensured that the therapeutic questions explored in later chapters remained clinically meaningful to the population for whom answers were sought.

The affective dimension of EB pain: more than skin deep

Recommendation: The affective and centrally mediated dimensions, including pain unpleasantness, nociplastic mechanisms, and psychosocial amplification of pain in EB should be explicitly recognised and incorporated into multidisciplinary pain management strategies.

A central finding of this thesis emerged from **Chapter 3**, in which the PQAS was applied to EB patients across all subtypes [89]. The PQAS assesses multiple pain qualities, comprising sensory characteristics, such as intensity, sharpness, and thermal qualities, and an affective dimension reflecting the degree to which pain is experienced as unpleasant. The affective quality of pain, the "unpleasantness" subscale, was scored highest and most consistently across EB subtypes, exceeding classic nociceptive and neuropathic descriptor scores in adults across all EB subtypes, a finding that is both clinically and theoretically significant.

Pain unpleasantness is functionally and neurobiologically distinct from pain intensity [49,81,99]. Whilst pain intensity is primarily encoded in somatosensory cortical brain regions, unpleasantness is processed in the anterior cingulate cortex (ACC), amygdala and insular cortex [50,105]. These are limbic and paralimbic structures governing affective and motivational responses to aversive stimuli, including pain [26]. The consistently high unpleasantness ratings observed in EB patients suggest that affective-motivational pain processing is amplified out of proportion to peripheral nociceptive or neuropathic drive, pointing toward central sensitisation (CS) of limbic pain pathways as a contributor to the overall pain burden.

Pain in EB typically presents as a mixed-pain state, suspected to comprise nociceptive, neuropathic, and nociplastic components. The nociceptive mechanism in EB is driven by low-threshold trauma to the skin and mucous membranes resulting in blister and wound formation. It may arise from daily mobility, inflammation, or from iatrogenic causes such as wound care and surgical procedures, among others [54,73,106]. Neuropathic contributions are supported by evidence of small fibre neuropathy (SFN) in recessive dystrophic EB (RDEB) and are probable in other EB subtypes [6]. SFN has been demonstrated histologically via intraepidermal nerve fibre density loss in RDEB skin biopsies, consistent with chronic nociceptive and inflammatory damage to peripheral sensory fibres; this neuropathic pain component can be effectively managed with pregabalin [11].

Nociplastic pain is distinguished from nociceptive pain by the absence of identifiable tissue pathology driving the pain signal, and from neuropathic pain by the absence of definable nerve damage. It reflects altered central processing, and more importantly manifests as the pain experience that is disproportionate to peripheral findings [23,49]. It is underpinned by CS, a state of enhanced excitability of nociceptive neurons in the spinal cord and brain [65,111]. The predominance of unpleasantness as the leading pain quality in EB is consistent with, though not in itself sufficient to confirm a nociplastic mechanism alongside previously established pain mechanisms in EB; unpleasantness should not be interpreted as a validated biomarker for CS in the absence of formal quantitative sensory testing-based (QST) phenotyping.

CS may manifest clinically as allodynia, hyperalgesia, temporal summation of pain, and persistent pain disproportionate to peripheral pathology [90]. In EB, repeated episodes of tissue injury, painful wound-care procedures, and chronic peripheral and systemic inflammation from infancy form precisely the conditions under which CS is known to develop [43,92]. This has yet to receive sufficient attention in the EB literature and warrants further scientific exploration.

Cognitive and affective factors further amplify the burden of pain in EB. Pain catastrophizing, anxiety, and depression are independently associated with amplified pain perception and reduced treatment responsiveness in chronic pain conditions and are prevalent amongst EB patients [24,25,56,58,59]. These cognitive-affective factors likely interact bidirectionally with persistent disease-related phenomena in EB, reinforcing a cycle of pain amplification that is not readily addressed by conventional analgesic strategies alone.

The mechanistic complexity of pain in EB carries direct implications for treatment. Conventional analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, target nociceptive pathways and do not fundamentally address the affective core of nociplastic or mixed-type pain. Yet, no EB-specific evidence currently exists for the concurring management of mixed-pain states, and treatment approaches must therefore be extrapolated from other chronic pain conditions; a gap that the subsequent chapters of this thesis begin to address, but do not fully resolve.

The findings in **Chapter 3** demonstrate that it is the affective dimension of pain that patients experience most prominently, and that conventional analgesics (as explored in **Chapter 2**) may be least equipped to address [75,91]. This provides a scientific rationale for pursuing treatments capable of modulating pain affect, among which CBMs represent a compelling and yet underexplored candidate [4,42,109,112]. CBMs exert their primary analgesic effects through CB1 and CB2 receptor-mediated pathways: CB1 receptors, concentrated in the ACC, amygdala, and descending pain-modulatory circuits, are particularly relevant to the modulation of pain affect, while CB2 receptors mediate peripheral inflammatory pathways exerting immunomodulatory effects [33,35,38,67,76,77,95,101,116].

PART II: CANNABINOID-BASED MEDICINES IN EPIDERMOLYSIS BULLOSA

Clinical observation of cannabinoid-based treatments

Recommendation: Anecdotal and survey-based evidence on cannabinoid-based medicines in EB should be interpreted within the evidence hierarchy and treated as hypothesis-generating rather than confirmatory.

The findings presented in Part I, particularly the predominance of pain unpleasantness, provided a scientific basis for investigating treatments capable of modulating centrally mediated pain, among which CBMs emerged as the primary candidate.

Prior to the studies presented in this thesis, CBM use in EB was mostly patient initiated, driven by informal knowledge exchange within patient communities and social media. Reports of symptomatic benefit had circulated widely; however, no clinical evidence existed to guide patients with EB or their clinicians. In the Netherlands, empirical prescription of CBMs had emerged, often as a last resort, based on extrapolated evidence from other chronic pain conditions, without formal evaluation in the context of EB pathomechanisms. Of note, the broad commercial and prescription availability of CBMs across many jurisdictions meant that patients suffering from a number of chronic conditions were increasingly accessing these treatments outside formal medical oversight [36,97]. In response, several clinical scientific groups sought to develop evidence-based practical guidelines to guide clinicians managing patients who had initiated or were considering CBMs, particularly for symptoms refractory to conventional therapies. Among these, MacCallum and Russo advocated a cautious titration approach to minimise adverse effect burden, given the availability of numerous CBM compositions, administration forms and doses, recommending that "*dose initiation should commence at modest levels, and titration of any cannabis preparation should be undertaken slowly over a period of as much as two weeks*" [53]; this and similar precautions, used in clinical practice, were incorporated into the design of the subsequent clinical trial in EB (**Chapters 6-8**).

Chapter 4 provided the first clinical documentation of prescribed CBM use in EB through a case series of three patients treated with pharmaceutical-grade sublingual THC/CBD oil at the University Medical Centre of Groningen (UMCG) [84]. All three patients reported reductions in pain severity and pruritus, and a decrease in concomitant analgesic use.

Whilst the generalisability of this three-patient case series is inherently limited, these observations established clinical plausibility and supported tolerability in a fragile patient population, and provided the first clinical experience with systemically (oromucosally) administered CBMs in EB. Since then, several case reports and prospective studies have documented comparable findings across adult and paediatric EB populations, including analgesia, pruritus amelioration, and improvements in wound healing and quality of life attributed to both analgesic and anti-inflammatory cannabinoid mechanisms [13,61,108]. The field received explicit recognition in the British Journal of Dermatology as warranting serious clinical investigation [57].

Chapter 5 extended the observational evidence through an international, cross-sectional survey of EB patients with CBM experience across five continents [87]. Seventy-one respondents who were either parents/caregivers of patients or patients themselves, reported using or having used CBMs, and the majority reported perceived benefits on pain, pruritus, sleep quality, and reduction in concomitant medication use. Patients reported additional improvements in wound healing, ability to move around, anxiety, overall mood and appetite, all important factors known to negatively impact quality of life in EB [19,27,40,68,74,93,100,113]. The geographic breadth and phenotypic diversity of the sample added a higher level of validity to the clinical observations reported in **Chapter 4**, albeit in the absence of rigorous scientific hypothesis testing. The limitations of this evidence must nonetheless be clearly acknowledged. Self-selected survey respondents disproportionately represent individuals with positive experiences [62]. This response bias is further compounded by the recognised under-publication of adverse and ineffective outcomes in cannabinoid research, a limitation that spans this field [31]. Additionally, placebo and expectation effects remain uncontrolled, and heterogeneity in products, doses, ratios, and routes of administration precluded conclusions about comparative efficacy [30]. Notably, the survey revealed that CBMs were being used in children with EB, underscoring both the urgency of rigorous research and the ethical imperative to provide evidence-based guidance to ensure safety when used, as a recent meta-analysis on 23 CBM-based randomized controlled trials (RCTs) declared significantly higher risks for adverse events in paediatric populations, versus adults [14].

Taken together, **Chapters 4** and **5** established that CBM use in EB was a widespread phenomenon that exceeded current evidence, identified pain

as the primary therapeutic target, and provided preliminary safety signals sufficient to inform the design of a controlled trial. These observational studies represent an appropriate evidence hierarchy: from case series to systematic survey, culminating in the controlled investigation described in **Chapters 6-8**.

The C4EB study: insights from a controlled design in an orphan disease

Recommendation: Randomised controlled trials in rare diseases require pragmatic, adaptive designs. Single-centre exploratory trials retain scientific value even when primary endpoints are not met.

Chapters 6, 7 and **8** describe the design and results of the C4EB study: a randomised, double-blind, placebo-controlled crossover trial of sublingual CBM-oil (Transvamix® [10% THC / 5% CBD]) for the management of chronic pain in EB [85,86]. The primary outcome was a 30% reduction in pain unpleasantness scores, specifically the affective quality subscale of the Short-Form McGill Pain Questionnaire-2 (SF-MPQ2), which is the dimension of pain demonstrated in **Chapter 3** to be most burdensome across EB subtypes. An fMRI substudy was incorporated to provide a neurobiological endpoint, evaluating whether combined THC and CBD modulate affective pain-processing.

Sublingual administration was selected for the C4EB study based on clinical familiarity from prior prescribing experience, pharmaceutical standardisation of the preparation, and its acceptability as a non-invasive, patient-friendly route.

The C4EB study demonstrated that a methodologically rigorous crossover design is feasible in an EB population, and this is itself a meaningful contribution. Additionally, this study is the first randomised, placebo-controlled trial of CBMs in EB, and the second clinical trial to date in EB assessing an analgesic intervention with pain as the primary outcome [11,80].

Clinical trials in rare diseases face complex challenges: restricted eligible populations, the ethical dilemmas of placebo administration in chronically suffering patients, logistical burden for physically impaired participants, and, specific to psychoactive interventions, the practical difficulty of maintaining blinding when participants may detect pharmacological effects through subjective central nervous system changes [63,78,83]. In

CBM trials, expectation and unmasking effects represent a recognised threat to internal validity, and their management in the C4EB design provides a documented framework for future research studies.

Near-term replication faces practical constraints, however. The eligible Dutch EB population is small, trial participation is burdensome, and prior trial participants may carry residual treatment expectations that could compromise outcome effects in subsequent studies. Multi-centre and international designs are therefore not merely desirable but arguably necessary for any adequately powered follow-up study.

The primary outcome was not met: sublingual CBM-oil did not produce a statistically significant reduction in pain affect compared to placebo. This result warrants contextualised interpretation. Five observations nuance the null primary finding.

I. First, a reduction in concomitant analgesic use was observed during the active treatment period, a clinically relevant signal consistent with the observational findings of **Chapters 4** and **5**.
II. Second, the adverse event profile of the CBM-oil administered as the intervention was mild and manageable in all participants, providing the first controlled safety data for sublingual CBMs in an EB cohort. This is supported by safety data for THC/CBD-based clinical studies in other chronic conditions [66,94,115].
III. Third, the exploratory sample size, a direct consequence of disease rarity and trial burden, limits statistical power and generalisability, and does not permit exclusion of a clinically meaningful pain-modulating effect.
IV. Fourth, the C4EB study maintained a high retention, with eight out of nine participants completing the full participation period (one drop-out occurred due to a protocol violation).
V. Lastly, for this trial a short semi-structured follow-up interview with participants provided several positive perspectives pertaining to CBMs as interventions in EB and perspectives on the trial methodology (unpublished): *"All eight participants supported continued CBM research in EB, with three explicitly willing to join a future study (A, D, F) and Participant B describing it (CBMs) as personally indispensable. Participants uniformly found the study feasible and well-organised, valued low barrier contact with the researcher, and made recurring calls for longer intervention phases and broader outcome measures encompassing itch, effects on skin and wounds, and sleep".*

Furthermore, the null primary result should be considered in the context of the pain mechanism hypothesis discussed in this thesis [23]. Nociplastic pain, characterised by chronically sensitised central circuits, and heavily influenced by psychological factors, may not be readily amenable to modulation within the sub-acute timeframe of a two-week crossover design. Unlike intrapulmonary administration of CBMs, which achieve peak plasma concentrations within minutes [107], sublingual administration reaches peak plasma levels in approximately 4.5 hours [41]. Coupled with the fact that THC and CBD response, and adverse-event onset, are dose-dependent [12], daily dose escalation for a period of up to two weeks was used during the C4EB study, conforming to regional best-practice and international recommendations on dose-titration [53]. Clinical evidence, however, in chronic pain intervention studies, assessing analgesic, non-analgesic, non-drug, system and educative interventions, suggests that treatment-related improvements are small at week 2, and peak at week 6 [45]. Whether cannabinoid-mediated modulation follows a similar timeline, and whether this relationship is dose-dependent, remains to be investigated, but may be a pitfall of the C4EB study.

The fMRI sub-study was a secondary outcome, included in **Chapter 8**. The Data Safety Monitoring Board approved enrolment of participants unable to undergo fMRI — whether due to contraindications or burden of scanning — prioritising contribution to the primary clinical endpoint at the expense of complete neuroimaging data. Hence, only three of eight participants consequently completed resting-state fMRI. Acquisition and analysis were fully feasible in all three participants, confirming for the first time that resting-state fMRI is practicable in an EB trial setting. Marked interindividual variability in functional connectivity across pain-relevant networks precluded group-level conclusions, likely reflecting the heterogeneity of EB subtypes, pain phenotypes, and prior cannabinoid exposure within this small cohort. These pilot data support the feasibility of resting-state fMRI as an objective neuroimaging endpoint in EB pain research, but realising this potential will require substantially larger cohorts for robust group-level inference [55]. The present dataset should therefore be interpreted strictly as proof-of-concept, not as evidence of treatment effect.

Taken together, these observations suggest that the null primary result should not be interpreted as evidence of CBM inefficacy, but rather that the C4EB design, while a meaningful first step, was not optimally configured to detect the analgesic signal that CBMs may provide in this pop-

ulation. Accordingly, the C4EB study should be regarded as informative rather than merely negative. In rare disease research, where each trial is resource-intensive, patient participation is finite, and the evidence base is sparse, a well-conducted feasibility study that generates controlled safety data, tests methodological assumptions, and advances mechanistic understanding represents an important contribution irrespective of the primary outcome. The successful execution of the C4EB study provides proof of concept and a template for future controlled research in EB. Alternative designs, including n-of-1 trials, are discussed further in Future Perspectives.

LIMITATIONS

The studies presented in this thesis share several limitations arising from the exploratory nature of the research programme and the inherent challenges of clinical investigation in a rare disease population. The following section highlights the predominant limitation themes throughout this thesis.

A fundamental limitation shared across all studies is sample size. EB affects an estimated 22 per million individuals in the Netherlands, with close to 500 patients registered at the UMCG, a population encompassing considerable molecular and phenotypic heterogeneity across EB subtypes [3]. Eligibility criteria for the C4EB study, including chronic pain, absence of CBM contraindications, willingness to undergo fMRI, and capacity for multiple in-person study visits, substantially reduced this already small pool. The trial was consequently restricted to an exploratory sample that limited statistical power and precluded subgroup analyses by EB subtype, demographics and baseline characteristics including pain catastrophizing, self-efficacy, CS, and anxiety and depressive symptoms. Subtype and sex-based analyses were nonetheless achievable in **Chapters 2** (n=68) and **3** (n=43), reflecting high participation rates among a patient community for whom the research carried direct relevance to daily life and care.

Pain is inherently subjective and known only to the person experiencing it — clinicians and researchers can therefore only infer the pain of others through reported measures and observable proxies [110]. Expectation and placebo effects further complicate interpretation in a clinical research context. Superimposed on these are the bio-psycho-social dynamics of

chronic pain, which fluctuates across temporal scales from moment to moment through to months — meaning any single measurement captures only a transient state within a continuously shifting experience. The fMRI sub-study was designed in part to address this through neurobiological correlates of pain and its modulation, objective biomarkers independent of verbal report, but these too are subject to temporal fluctuations not captured in a single imaging session (±1 hour versus two weeks of intervention exposure, as in Chapter 7) [55].

No formal characterisation of pain mechanism was performed in any study in this thesis. QST, particularly pain-threshold testing, and validation of the Central Sensitisation Inventory (CSI) in an EB cohort could have contributed to raise the probability of identifying nociplastic pain mechanisms and CS in individual participants [70]. The nociplastic hypothesis discussed throughout this thesis therefore rests on indirect clinical and qualitative evidence. Without such assessments, it cannot be confirmed at the mechanistic level. Methodologically appropriate research combining these tools in EB populations is required for pain phenotyping, building on the hypothesis-generating foundations in this thesis.

The application of the PBI in **Chapter 2** carries several methodological limitations. The PBI-S was designed for paired pre- and post-intervention administration; the pre-intervention component was omitted in this study, and the instrument was applied to general clinical care rather than a defined treatment, preventing attribution of reported benefit to any specific intervention. The PBI has not been validated for use in EB, and its standardised item set likely underrepresents concerns central to EB, including wound-care burden, procedural pain, and mucosal involvement. Validating an EB-specific PBI could play an important role in patient-weighted outcome measurements for EB research and clinical practice, similar to PBI validation for other conditions [1,2,7,8,20,114].

A further consideration concerns the basis for selecting the CBM composition and route of administration of the intervention tested in **Chapter 7**. The CBM-oil administered has a fixed-ratio, pharmaceutical-grade preparation administered by sublingual route following standardised dose-escalation. The international survey in **Chapter 5** documented considerable diversity in real-world CBM use amongst EB patients, including topical application directly to wounds and painful skin [87]. Topical CBMs may act via peripheral cannabinoid receptor activation at the wound site

[5,102], with a mechanistic profile distinct from systemic administration and without the central pharmacological effects associated with sublingual delivery. Given the mixed-pain character of EB and the breadth of central analgesic and peripheral immunomodulatory properties of cannabinoids [18,69], topical administration represents a therapeutically distinct and yet untested intervention strategy in this population.

Expectation and placebo effects also constitute an important limitation specific to CBM research. CBMs carry a distinctly prominent public and cultural profile, associated in popular discourse with therapeutic potential, natural treatment, and patient empowerment, that may generate strong positive expectations prior to and during treatment[29]. Interestingly, in the C4EB study, seven of eight participants reported greater global pain improvement (SF-MPQ2 global score) during the first administered intervention, independent of whether they received CBM or placebo, an effect plausibly attributable to positive treatment expectation. Performing multiple crossovers, may offer a partial solution by cancelling out expectation and placebo effects.

Predictors of CBM response in EB remain poorly defined. The most mechanistically coherent approach would be to align the pathobiological drivers of EB pain with the pain-alleviating pathways targeted by cannabinoids, yet it remains unclear which EB subtypes, based on their underlying molecular pathology, or which baseline characteristics, are most likely to predict a favourable response. This gap limits both patient selection and trial stratification. In this context, the absence of pharmacogenetic profiling requires genuine consideration. No genotyping was performed, meaning inter-individual variability in THC and CBD metabolism via CYP2C9, CYP3A4, and CYP2C19 cannot be accounted for [96,104]. Pharmacogenetic profiles may have played a role in the observed marked variability in dose achieved during titration in the C4EB study, where several participants reached the maximum permitted dose by day 14 with minimal or no adverse events, while others were limited at substantially lower doses as early as day 2. Poor metabolisers accumulate higher THC concentrations at lower doses, increasing adverse event likelihood and capping the achievable dose, while rapid metabolisers may require higher doses to reach therapeutic plasma levels where a maximum titration protocol dose may be considered insufficient. Without pharmacogenetic data, true non-responders cannot be distinguished from the remaining cohort [79].

A related constraint concerns the washout period between crossover arms in **Chapter 7** [51]. THC is highly lipophilic and accumulates in adipose tissue during daily dosing [41]. Following two weeks of active treatment, residual THC or CBD and their pharmacologically active metabolites may persist beyond the washout window, meaning participants who received the active arm first may not have returned to a true pharmacological baseline before commencing the placebo period. Urine toxicology was negative for THC in all the samples collected during placebo phases. However, standard immunoassay screens operate at a lower limit of quantification that may not detect trace or sub-threshold residual concentrations sufficient to exert a pharmacological effect. Plasma THC sampling at the start of each treatment period would provide a more sensitive index of pharmacological washout but was omitted to minimise EB participant risks and harms in this study.

FUTURE PERSPECTIVES

Several directions for future research emerge from this thesis.

The role of nociplasticity and central sensitisation in EB pain warrants dedicated investigation. Future studies should prioritise formal pain phenotyping across EB subtypes, with stratification by sex and age, to close the mechanistic gap identified above. Identifying patients with a predominant nociplastic phenotype would serve a dual purpose: building the mechanistic evidence base and enabling phenotype-based recruitment in future trials, substantially improving sensitivity to detect treatment effects. The affective pain quality predominance identified in **Chapter 3** further underscores this need, psychosocial drivers of nociplastic pain, including catastrophising, anxiety, depression, and sleep disturbance, have not been systematically examined in EB [24,56]. Rigorous pain phenotyping should therefore inform not only trial design but also multidisciplinary pain management, incorporating pharmacological, psychosocial, and lifestyle-based approaches that are well-established in other chronic pain conditions but remain uninvestigated in EB [49].

Future EB clinical trials should consider designs beyond the conventional RCT. Given the rarity of EB, substantial between-patient heterogeneity, and the likelihood that treatment responses differ by pain phenotype and molecular subtype, group-level analyses risk obscuring effects that are real and clinically significant at the individual level. N-of-1 trials,

employing within-patient randomisation across multiple crossover periods, are particularly well suited to this context. They preserve statistical rigour while accommodating small populations and can detect responses that group designs would average out [17]. Multi-centre and international collaborative designs offer a complementary solution by expanding the eligible population and improving generalisability, with existing networks providing a ready infrastructure for such collaboration.

The optimal composition, dose, and route of CBM administration for EB pain management remain undetermined. Systematic dose-finding studies, comparative trials of sublingual versus topical formulations, opioids versus cannabinoids, and pharmacokinetic investigations in EB patients, who may have substantially altered absorption due to compromised skin, chronic inflammation, and pharmacogenetic profiles are warranted. Guided titration protocols provide a structured framework for individualising CBM treatment in clinical practice and generating comparative real-world evidence, but achieving more predictable dosing and effects is paramount to treatment milestones in EB.

Beyond pain, the potential role of CBMs in EB warrants separate investigation. Cannabinoids exert well-documented anti-inflammatory and immunomodulatory effects through CB2 receptor-mediated pathways, and preliminary evidence suggests that topical CBD may support wound healing and reduce skin inflammation and pruritus. Given that wound burden in EB is both a primary source of nociceptive input and a central determinant of quality of life, prospective studies examining CBM effects on wound healing, skin integrity, and systemic inflammation would substantially broaden the evidence base for cannabinoid use in this condition and may open additional therapeutic avenues beyond analgesia.

A preventive perspective deserves greater prominence in future EB pain research. The trajectory from recurrent nociceptive input to established CS is not inevitable, and early, adequate analgesia may reduce the probability of nociplastic transition in vulnerable individuals [43,92]. Current analgesic strategies in EB, predominantly paracetamol, NSAIDs, and opioids, are often insufficient, as was reflected in PBI findings that pain remained the leading unmet need despite existing treatment. Future research should therefore investigate whether timely nociceptive pain control, combined with psychosocial and lifestyle interventions, can meaningfully modify the nociplastic trajectory in EB, positioning pain management not only as symptomatic treatment but as a preventive

strategy against chronic nociplastic pain. Additionally, opioid-sparing effects should be investigated. Pre-clinical and observational studies suggest that morphine requirements can be reduced approximately 3.5-fold when co-administered with the cannabinoid THC. A recent study confirmed similar effects with coadministration of THC/CBD but noted a higher overall drug load [16]. The broader data on CBM-based opioid-sparing, however, remains inconclusive [71,72].

Future CBM and pain trials in EB should align their outcome selection with COSEB, as these outcome tools are developed and homogenised. Harmonisation of primary and secondary endpoints across EB trials would facilitate cross-study comparison, enable meta-analysis, and ensure that trial results are interpretable in the context of the broader EB evidence base.

A distinct and underexplored research question emerging from this thesis concerns whether selectively reducing pain unpleasantness (versus intensity) constitutes a clinically meaningful treatment goal in its own right. In chronic pain conditions dominated by affective-motivational pain processing, reducing perceived unpleasantness may improve quality of life, emotional wellbeing, and functional capacity even in the absence of intensity reduction. Future trials in EB should measure these outcomes independently and assess their relative contribution to patient-reported benefit.

In summary, the ideal EB-pain clinical trial would recruit a carefully selected subpopulation whose pain phenotype maps to cannabinoid mechanisms of action, confirmed through baseline quantitative sensory testing and pharmacogenetic profiling, and powered through international multi-centre collaboration to enable subgroup analyses by EB subtype and molecular pathology. It would incorporate outcomes anchored to COSEB endpoints weighted by patient-defined priorities, continuous pharmacokinetic sampling, optional neuroimaging substudies, and undergo multiple crossovers. A combination that EB's rarity and heterogeneity make extraordinarily difficult to realise — but the infrastructure, the endpoints, the patient community and financing to support such a trial are, for the first time, beginning to take shape.

Concluding Remarks

This thesis demonstrates that pain in EB is complex, multidimensional, and inadequately addressed by current diagnostic and therapeutic strat-

egies. Patient perspectives, systematically captured and centrally positioned throughout this research programme, consistently identified pain as the dominant unmet need. Applying the PBI and PQAS to EB populations, this thesis established both the importance of pain as a therapeutic priority and the predominance of its affective dimension across all EB subtypes. These are findings that point toward central and nociplastic mechanisms as under-recognised contributors to the EB pain experience and deserve greater attention. Real-world CBM use, documented through a case series and an international survey, demonstrated clinical plausibility, identified pain as the primary therapeutic target, and provided the safety signals necessary to justify a controlled trial. The C4EB study did not demonstrate a statistically significant effect on pain affect, but established trial feasibility, provided controlled safety data, and generated mechanistic hypotheses to inform future research. Taken together, this thesis contributes a patient-centred evidence base for CBMs in EB, reframes pain in this population as a mixed-type experience requiring multimodal therapeutic engagement, and underscores that effective management will demand not only pharmacological innovation but a deeper, more systematic engagement with pain phenotyping and the central and affective mechanisms that underpin the EB pain experience.

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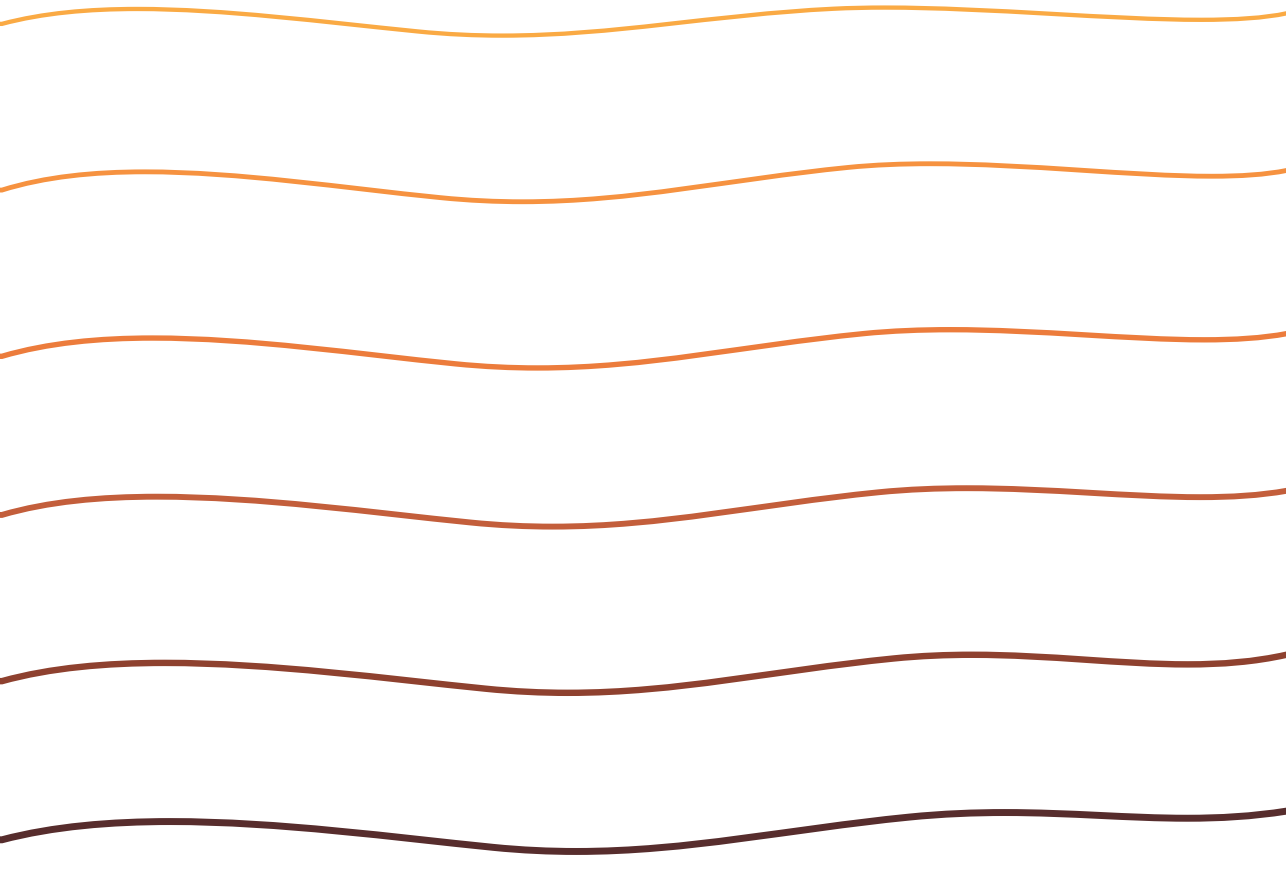
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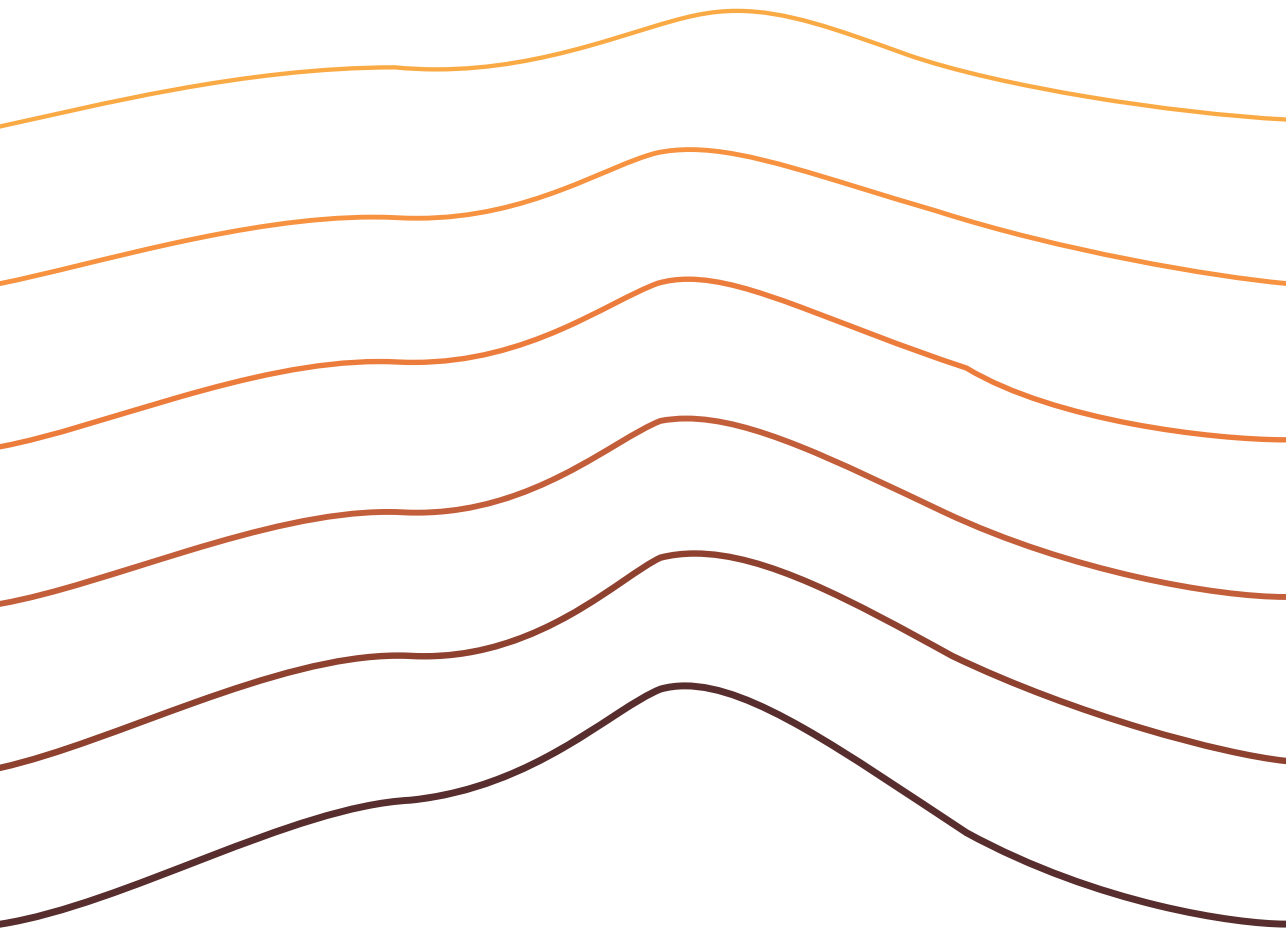
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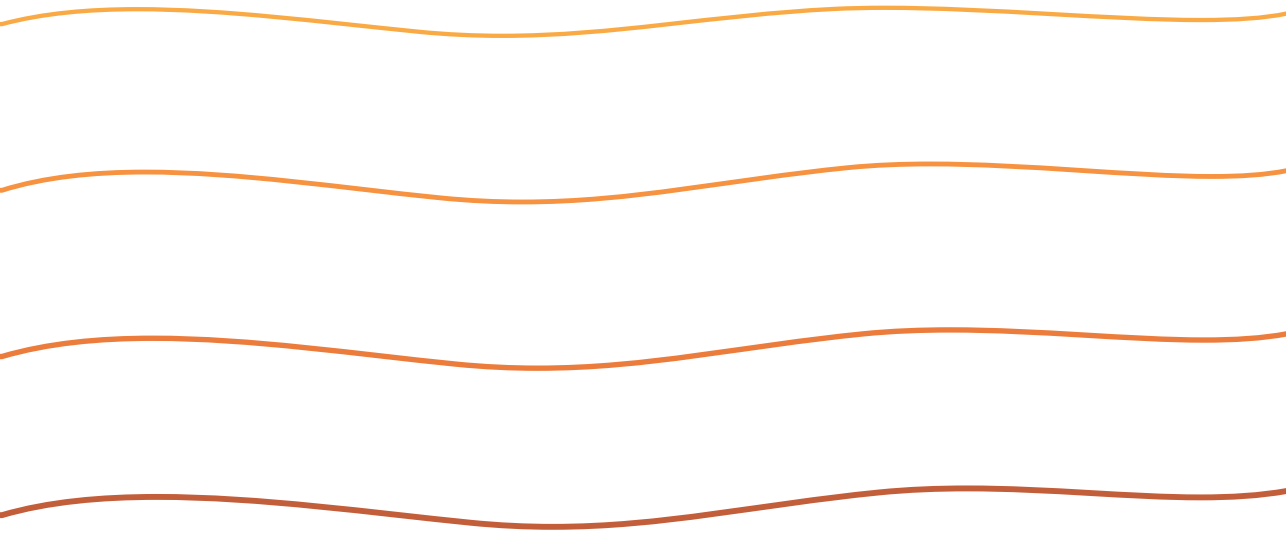
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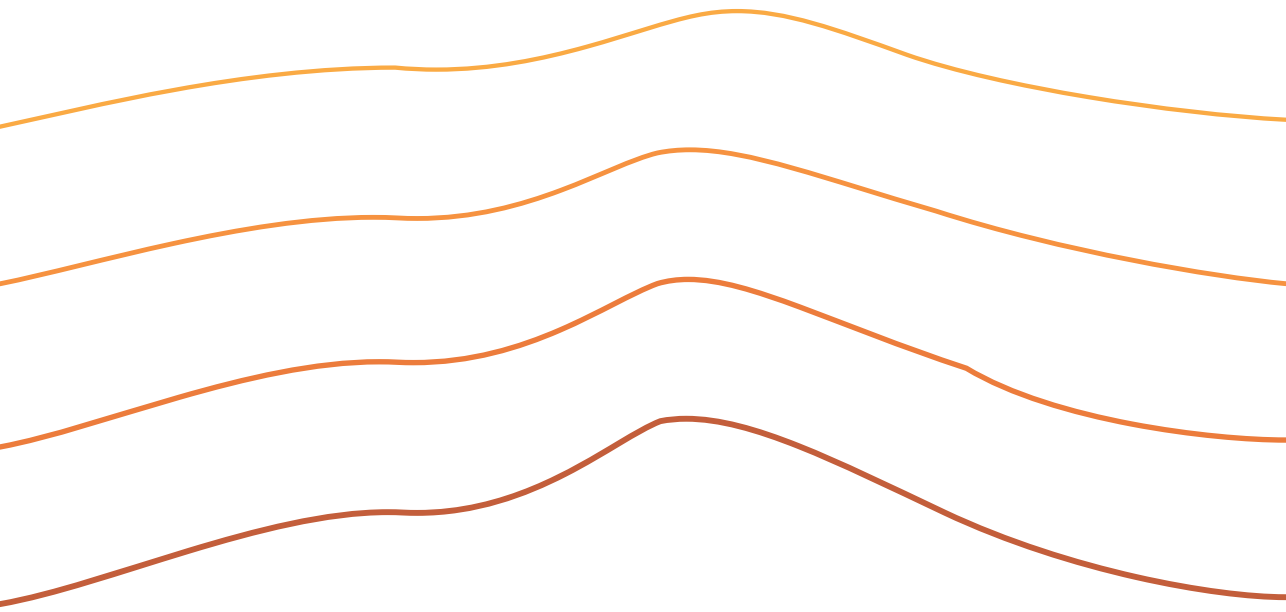
Appendices





Layperson Summary

Lekensamenvatting



LAYPERSON SUMMARY

Beyond the Blister: Cannabinoids for Pain in EB

WHAT WE LEARNED AND WHY IT MATTERS

EB pain is more complex than it looks — and it has been underestimated

Anyone living with EB, or caring for someone who does, knows that pain is relentless. What this research found is that EB pain comes from at least three different sources at once: pain from wounds and dressings, pain from damaged nerve fibres, and pain that becomes amplified by the brain and nervous system over time. That third type, where the nervous system itself becomes oversensitised, helps explain why EB pain can feel so overwhelming even on a "good skin" day, and why it so often does not respond to ordinary painkillers. Recognising this has real consequences: it means that treating the wounds alone is not enough, and that the nervous system itself needs to be part of the treatment plan.

Patients told us cannabis-based medicines helped — across the board

In a survey of 71 EB patients from five continents, nearly all of those who had tried cannabis-based medicines (CBMs) reported real improvements — in pain (94%), itch (91%), wound healing (81%), and overall wellbeing (95%). Strikingly, almost four in five had been able to cut down or stop other pain medications as a result. These are not small numbers, and they span exactly the things that patients in a separate study said mattered most to them: less pain, less itch, better skin. Side effects were mild, the most common being a dry mouth.

A clinical trial showed encouraging signals, even if it didn't hit its main target.

Eight adults with EB took part in a rigorous, placebo-controlled clinical trial of sublingual THC/CBD oil (Transvamix). The trial did not reach its primary statistical goal — partly because the group was small, and partly because this type of pain likely needs longer treatment to fully respond. But the signals that did emerge were striking: three-quarters of participants experienced a meaningful reduction in overall pain with the active medicine, compared to half with placebo. Most importantly, half of

all regular pain medications were stopped during the CBM phase. Not a single one was stopped during the placebo phase. The medicine was well tolerated throughout.

This is the beginning, not the end

This research has built the scientific foundation for the next generation of EB pain trials. Cannabis-based medicines are not yet a cure, and they are not right for everyone — but the evidence consistently points in the same direction: they reduce pain, reduce itch, reduce the need for other medications, and are well tolerated. What is now needed are larger, longer trials with more participants across more EB subtypes. Patients and families who have lived this experience every day deserve treatments backed by the strongest possible evidence. This thesis is a step toward making that happen.

VOORBIJ DE BLAAR: CANNABINOÏDEN VOOR PIJN BIJ EB

Wat We Hebben Geleerd en Waarom Het Ertoe Doet

EB-pijn is complexer dan het lijkt — en is onderschat

Iedereen die met EB leeft, of voor iemand zorgt die dat doet, weet dat pijn onverbiddelijk is. Dit onderzoek toont aan dat EB-pijn tegelijkertijd uit minimaal drie verschillende bronnen kan komen: pijn door wonden en verbanden, pijn door beschadigde zenuwvezels, en pijn die door de hersenen en het zenuwstelsel in de loop van de tijd wordt versterkt. Dat derde type, waarbij het zenuwstelsel zelf overgevoelig wordt, verklaart waarom EB-pijn zo overweldigend kan aanvoelen, zelfs op een "goede huid"-dag, en waarom gewone pijnstillers zo vaak weinig effect hebben. Het erkennen hiervan heeft reële gevolgen: het betekent dat alleen de wonden behandelen niet voldoende is, en dat het zenuwstelsel zelf onderdeel moet zijn van het behandelplan.

Patiënten vertelden ons dat medicinale cannabinoïden hielpen — op alle fronten

In een enquête onder 71 EB-patiënten van vijf continenten rapporteerden bijna alle deelnemers die medicinale cannabinoïden (CBM's) hadden geprobeerd echte verbeteringen — in pijn (94%), jeuk (91%), wondgenezing (81%) en algeheel welzijn (95%). Opvallend genoeg had bijna vier op de vijf andere pijnmedicatie kunnen verminderen of stoppen. Dit zijn geen kleine aantallen, en ze beslaan precies de domeinen die patiënten in een apart onderzoek als het belangrijkst aangaven: minder pijn, minder jeuk, betere huid. Bijwerkingen waren mild; de meest voorkomende was een droge mond.

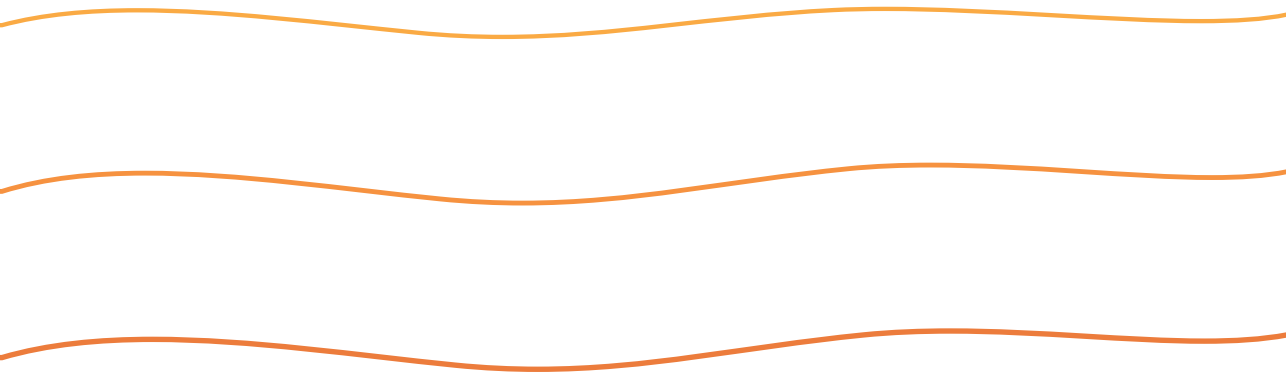
Een klinische studie liet veelbelovende resultaten zien, ook al werd het hoofddoel niet bereikt.

Acht volwassenen met EB namen deel aan een strenge, placebogecontroleerde klinische studie met sublinguaal THC/CBD-olie (Transvamix). De studie bereikte haar primaire statistische doel niet — deels omdat de groep klein was, en deels omdat dit type pijn waarschijnlijk een langere behandeling nodig heeft om volledig te reageren. Maar de signalen die wel naar voren kwamen waren opvallend: driekwart van de deelnemers

ervoer een betekenisvolle vermindering van de algehele pijn met het actieve medicijn, vergeleken met de helft bij placebo. Het meest opvallend was dat de helft van alle reguliere pijnmedicatie werd gestopt tijdens de CBM-fase. Niet één enkel medicijn werd gestopt tijdens de placebofase. Het medicijn werd gedurende de gehele studie goed verdragen.

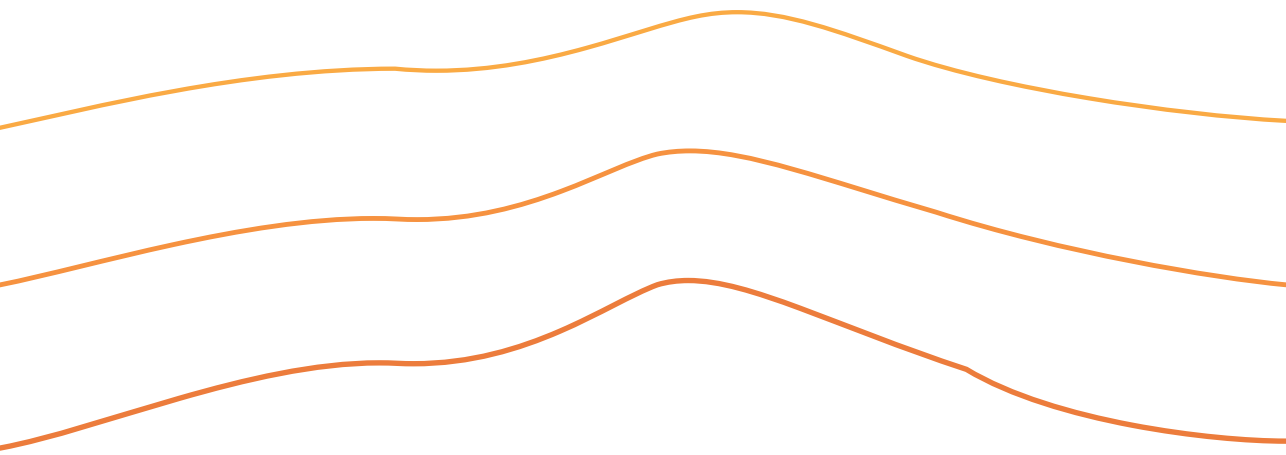
Dit is een begin, geen einde

Dit onderzoek heeft de wetenschappelijke basis gelegd voor de volgende generatie EB-pijnstudies. Medicinale cannabinoïden zijn nog geen geneesmiddel, en ze zijn niet voor iedereen geschikt — maar het bewijs wijst consequent in dezelfde richting: ze verminderen pijn, verminderen jeuk, verminderen de behoefte aan andere medicijnen en worden goed verdragen. Wat nu nodig is, zijn grotere, langere studies met meer deelnemers en meer EB-subtypes. Patiënten en families die deze ervaring elke dag meemaken, verdienen behandelingen die op het sterkst mogelijke bewijs zijn gebaseerd. Dit proefschrift is een stap in die richting.



Scientific Summary

Wetenschappelijke Samenvatting



ENGLISH SUMMARY

Background and Aims

Epidermolysis bullosa (EB) is a rare, inherited skin fragility disorder characterised by blistering, chronic wounds, and lifelong multisystem complications. Pain is consistently ranked as the most debilitating burden of the disease. It is not a single phenomenon: it arises from tissue damage and wound care (nociceptive pain), from dysfunctional or damaged neurons (neuropathic pain), and, as this thesis argues, from central amplification mechanisms that sustain pain beyond what tissue pathology alone can explain (nociplastic pain). Despite this burden, evidence-based analgesic strategies remain inadequate. Cannabinoid-based medicines (CBMs) represent a biologically plausible treatment candidate, given that the endocannabinoid system modulates pain, inflammation, and itch at multiple levels of the nervous system. This thesis characterises EB pain with greater precision and constructs a stepwise evidence base for CBM efficacy and tolerability, centred on the affective dimension of pain as a primary therapeutic target.

Chapter 2 - What EB Patients Need Most

A systematic needs assessment using the Patient Benefit Index for Skin diseases (PBI-S) was conducted in 68 patients with EB. The four highest-ranking unmet treatment needs were: to get better skin quickly, to be healed of all skin alterations, to be free of itching, and to be free of pain. Pain correlated positively with all 25 assessed patient needs across the questionnaire, demonstrating its pervasive impact on every domain of wellbeing and providing the empirical justification for positioning pain as the primary therapeutic target throughout the thesis.

Chapter 3 - The Character of EB Pain

The Pain Quality Assessment Scale (PQAS) was administered to 43 patients with EB. Ninety-one percent reported pain, with neuropathic features, including burning, stabbing, and electric shock sensations, especially prominent in RDEB and JEB. Notably, pain unpleasantness was consistently the highest-rated pain quality across most subtypes, often exceeding intensity scores. This matters: unpleasantness captures the affective, suffering dimension of pain, and its prominence suggests that central processing mechanisms play a key role in EB pain, pointing toward a mechanistic picture that goes beyond nociception alone.

Chapter 4 - First Clinical Signals

Three patients with different EB subtypes, each with their own complex and individually tailored analgesic regimen, were treated with sublingual THC/CBD oil (Transvamix) in a supervised, physician-led clinical setting with careful dose titration. Despite differences in diagnosis and prior medication history, all three experienced substantial and sustained improvements in pain, reductions in pruritus, and a marked analgesic-sparing effect including weaning from opioid medications. The treatment was well tolerated in all cases. These observed outcomes under medical supervision provided a credible rationale to pursue further investigation of this treatment modality.

Chapter 5 - Real-World Evidence

An international online survey was completed by 71 EB patients or their caregivers from five continents. The breadth of reported benefit from CBM-use is striking: 95% reported improvement in overall EB symptoms, 94% in pain, 91% in pruritus, and 81% in wound healing, spanning the exact domains patients had identified as their most important needs in Chapter 2. Seventy-nine percent had reduced or discontinued conventional analgesic medications. Only 24% of CBM-use was prescribed by doctors. Self-reported side-effects were minimal; the most common was dry mouth (44%), and no serious adverse events from CBM-use were reported by respondents.

Chapter 6 - Designing a Rigorous Trial in a Rare Disease

The protocol for the C4EB randomised controlled trial is described. The trial was designed as a double-blind, placebo-controlled crossover study evaluating sublingual Transvamix (10% THC, 5% CBD) in adult patients with EB, with functional MRI (fMRI) incorporated as an exploratory outcome to assess CBM effects on central pain processing networks. The protocol addresses the specific methodological challenges of conducting rigorous interventional research in a rare and heterogeneous patient population.

Chapters 7 & 8 - The C4EB Study: Results

Eight adult patients with EB completed the trial. The primary outcome, a statistically significant improvement in the pain affect domain of the short-form McGill Pain Questionnaire (SF-MPQ2), was not achieved, and pain unpleasantness did not significantly decrease versus placebo. This must be understood in context: the sample was small, the crossover period short, and nociplastic pain mechanisms likely require longer treatment windows to engage. Clinically meaningful signals nonetheless

emerged: 75% of participants achieved a ≥30% reduction in overall pain with CBMs versus 50% with placebo. Half of all analgesics were discontinued during the CBM phase; all were continued during placebo, a striking analgesic-sparing effect. The fMRI sub-study was feasible and well tolerated, providing preliminary evidence of heterogeneous changes in central pain network connectivity after CBM administration. The adverse event profile was favourable throughout.

Chapter 9 - Synthesis and Implications

The Discussion integrates the thesis findings into a mechanistic account of EB pain as nociceptive, neuropathic, and likely nociplastic in nature, arguing that repeated tissue injury, chronic inflammation, and the psychological burden together drive a pain experience that nociceptive-directed treatments cannot adequately address. Across the case series, and international cross-sectional survey, patients consistently reported benefits from CBMs on multiple domains known to affect quality of life in EB. Drawing on the broader CBM literature, it is proposed that cannabinoids may preferentially modulate affective pain pathways, offering a mechanistic explanation for the clinically meaningful signals observed, despite the primary endpoint not being met in the C4EB study. Importantly, the C4EB study is framed as informative rather than merely negative: it provides proof of concept for a controlled design in EB, generates the first controlled safety data for sublingual CBMs in this population, and demonstrates for the first time that patients with EB can safely undergo resting-state fMRI in a trial setting. Timely nociceptive pain control may also help prevent nociplastic transition, positioning effective analgesia early on as a potentially disease-modifying strategy.

CONCLUSION

Pain in EB is severe, multidimensional, and undertreated. This thesis maps the breadth of its burden and homes in on affective and nociplastic dimensions that nociception-focused treatments cannot fully address. Although the C4EB study did not meet its primary endpoint, cannabinoid-based medicines demonstrated consistent signals across analgesic sparing, global pain reduction, and patient-reported benefit, with a tolerability profile that supports continued clinical consideration. What is now needed are trials that are mechanistically precise, adapted to rare disease constraints, and anchored in outcomes that patients experience as meaningful.

NEDERLANDSTALIGE SAMENVATTING

Achtergrond en Doelstellingen

Epidermolysis bullosa (EB) is een zeldzame, erfelijke huidfragiliteitsaandoening die wordt gekenmerkt door blaarvorming, chronische wonden en levenslange multisysteemcomplicaties. Pijn wordt consequent beschouwd als de meest invaliderende last van de ziekte. Het is geen enkelvoudig fenomeen: het ontstaat door weefselschade en wondverzorging (nociceptieve pijn), door disfunctionerende of beschadigde neuronen (neuropathische pijn), en, zoals dit proefschrift betoogt, door centrale amplificatiemechanismen die pijn in stand houden voorbij wat weefselschade alleen kan verklaren (nociplastische pijn). Ondanks deze last blijven op evidence gebaseerde analgetische strategieën ontoereikend. Cannabinoïd gebaseerde medicijnen (CBMs) vormen een biologisch plausibele behandelingskandidaat, gegeven dat het endocannabinoïdesysteem pijn, ontsteking en jeuk moduleert op meerdere niveaus van het zenuwstelsel. Dit proefschrift karakteriseert EB-pijn met grotere precisie en construeert een stapsgewijze evidence base voor de werkzaamheid en verdraagbaarheid van CBMs, gecentreerd op de affectieve dimensie van pijn als primair therapeutisch doel.

Hoofdstuk 2 – Wat EB-patiënten het meest nodig hebben

Een systematische behoeftenanalyse met behulp van de Patient Benefit Index voor Huidziekten (PBI-S) werd uitgevoerd bij 68 patiënten met EB. De vier hoogst gerangschikte onvervulde behandelingsbehoeften waren: snel betere huid krijgen, genezen worden van alle huidafwijkingen, vrij zijn van jeuk en vrij zijn van pijn. Pijn correleerde positief met alle 25 beoordeelde patiëntbehoeften in de vragenlijst, wat de alomtegenwoordige impact ervan op elk domein van welzijn aantoont en de empirische rechtvaardiging biedt voor het positioneren van pijn als het primaire therapeutische doel gedurende het gehele proefschrift.

Hoofdstuk 3 – Het karakter van EB-pijn

De Pain Quality Assessment Scale (PQAS) werd afgenomen bij 43 patiënten met EB. Eenennegentig procent rapporteerde pijn, met neuropathische kenmerken, waaronder brandende, stekende en elektrische schoksensaties, die vooral opvallend waren bij RDEB en JEB. Opvallend was dat pijnonaangenaamheid consequent de hoogst beoordeelde pijnkwaliteit was over de meeste subtypen, en daarbij vaak de intensiteitsscores overtrof. Dit is van belang: onaangenaamheid omvat de affectieve, lijdensdimensie van pijn, en de prominentie ervan suggereert dat centrale

verwerkingsmechanismen een sleutelrol spelen in EB-pijn, wijzend op een mechanistisch beeld dat verder gaat dan nociceptie alleen.

Hoofdstuk 4 – Eerste klinische signalen

Drie patiënten met verschillende EB-subtypen, elk met hun eigen complexe en individueel afgestemde analgetische behandeling, werden behandeld met sublinguale THC/CBD-olie (Transvamix) in een begeleide, door een arts geleide klinische setting met zorgvuldige dosistitratie. Ondanks verschillen in diagnose en voorafgaande medicatiegeschiedenis ervoeren alle drie substantiële en aanhoudende verbeteringen in pijn, reducties in pruritus en een uitgesproken analgesiebesparend effect, waaronder het afbouwen van opioïde medicatie. De behandeling werd in alle gevallen goed verdragen. Deze geobserveerde uitkomsten onder medisch toezicht boden een geloofwaardige rationale om verder onderzoek naar deze behandelingsmodaliteit na te streven.

Hoofdstuk 5 – Bewijs uit de klinische praktijk

Een internationale online enquête werd ingevuld door 71 EB-patiënten of hun verzorgers van vijf continenten. De breedte van de gerapporteerde baten van CBM-gebruik is opvallend: 95% rapporteerde verbetering in algehele EB-symptomen, 94% in pijn, 91% in pruritus en 81% in wondgenezing, omspannend precies de domeinen die patiënten als hun meest belangrijke behoeften hadden geïdentificeerd in Hoofdstuk 2. Negenenzeventig procent had conventionele analgetische medicatie verminderd of gestopt. Slechts 24% van het CBM-gebruik was voorgeschreven door artsen. Zelfgerapporteerde bijwerkingen waren minimaal; de meest voorkomende was een droge mond (44%), en geen ernstige ongewenste voorvallen van CBM-gebruik werden door respondenten gerapporteerd.

Hoofdstuk 6 – Het ontwerpen van een rigoureus onderzoek bij een zeldzame ziekte

Het protocol voor de C4EB gerandomiseerde gecontroleerde studie wordt beschreven. De studie was ontworpen als een dubbelblind, placebogecontroleerd cross-overstudieontwerp dat sublinguale Transvamix (10% THC, 5% CBD) evalueerde bij volwassen patiënten met EB, met functionele MRI (fMRI) opgenomen als exploratieve uitkomst om CBM-effecten op centrale pijnverwerkingsnetwerken te beoordelen. Het protocol adresseert de specifieke methodologische uitdagingen van het uitvoeren van rigoureus interventioneel onderzoek in een zeldzame en heterogene patiëntenpopulatie.

Hoofdstukken 7 & 8 – De C4EB-studie: Resultaten

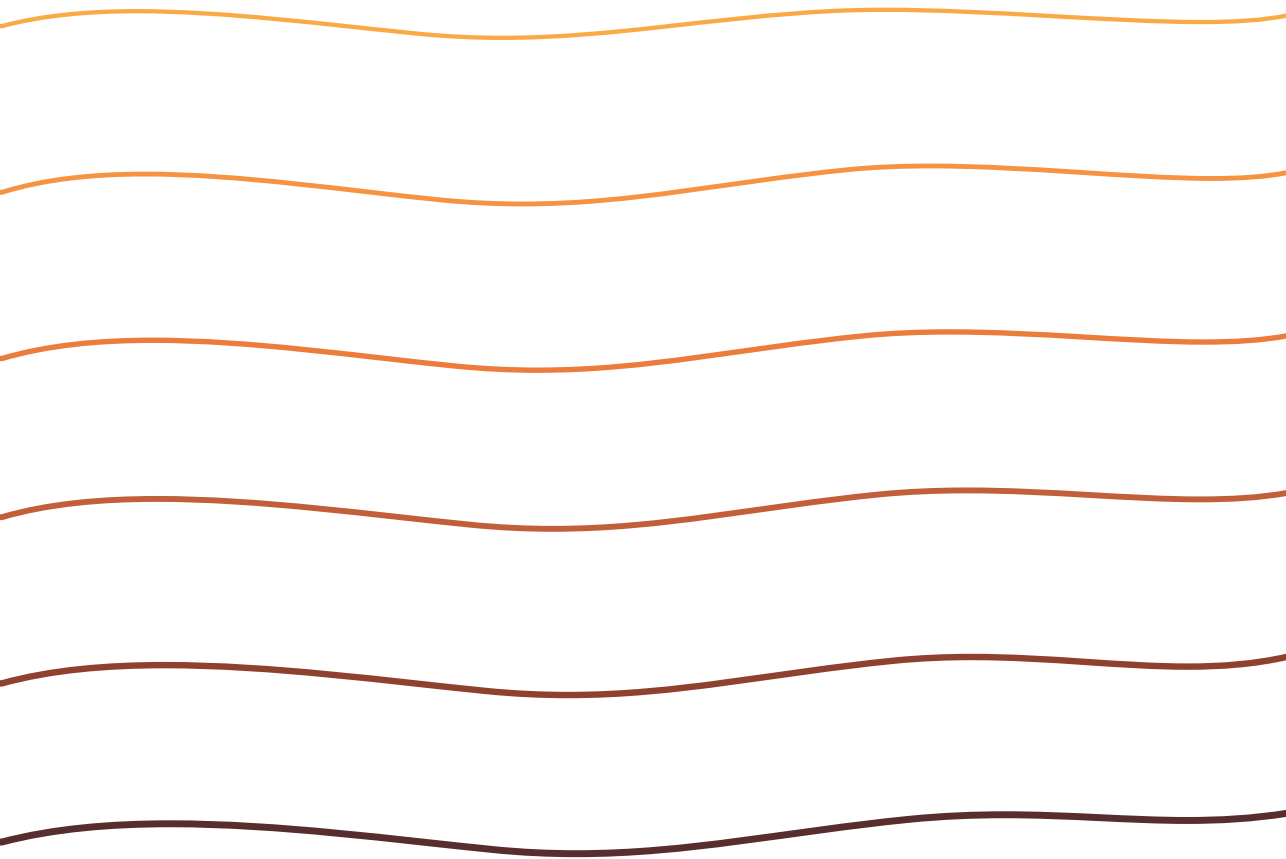
Acht volwassen patiënten met EB voltooiden de studie. De primaire uitkomst, een statistisch significante verbetering in het pijnaffectdomein van de korte versie van de McGill Pain Questionnaire (SF-MPQ2), werd niet bereikt en pijnonaangenaamheid verminderde niet significant ten opzichte van placebo. Dit moet in context worden begrepen: de steekproef was klein, de cross-overperiode was kort, en nociplastische pijnmechanismen vereisen waarschijnlijk langere behandelingsvensters om effect te sorteren. Klinisch betekenisvolle signalen kwamen desalniettemin naar voren: 75% van de deelnemers bereikte een ≥30% reductie in algehele pijn met CBMs versus 50% met placebo. De helft van alle analgetica werd gestopt tijdens de CBM-fase; alle werden voortgezet tijdens placebo, een opvallend analgesiebesparend effect. De fMRI-substudie was haalbaar en goed verdragen, en leverde voorlopig bewijs van heterogene veranderingen in de connectiviteit van centrale pijnnetwerken na CBM-toediening. Het bijwerkingenprofiel was gedurende de gehele studie gunstig.

Hoofdstuk 9 – Synthese en implicaties

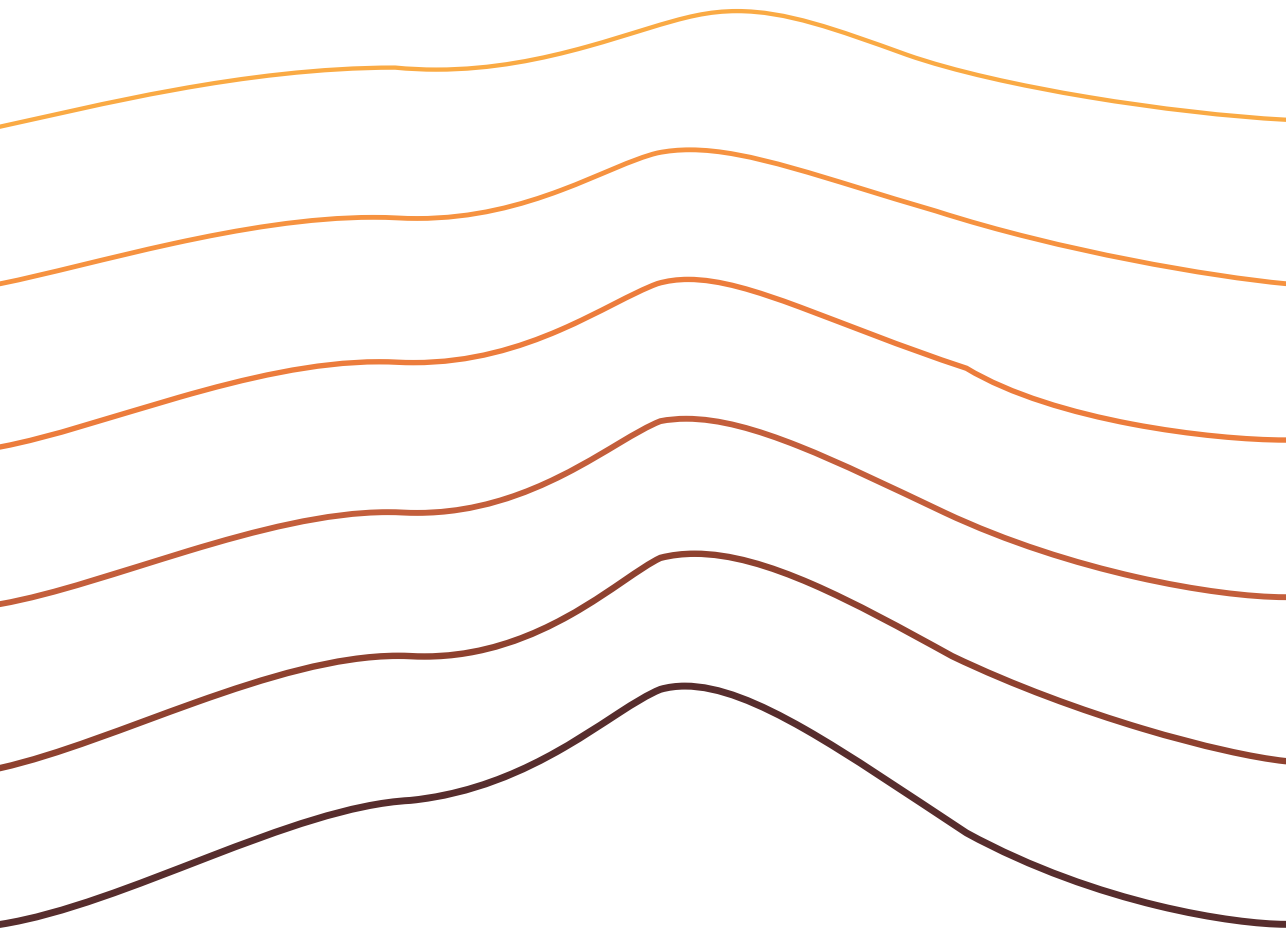
De discussie integreert de bevindingen van het proefschrift in een mechanistisch beeld van EB-pijn als nociceptief, neuropathisch en waarschijnlijk nociplastisch van aard, met het argument dat herhaald weefselletsel, chronische ontsteking en de psychologische last samen een pijnervaring veroorzaken die door nociceptie-gerichte behandelingen niet adequaat kan worden aangepakt. Uit de casusreeks en de internationale cross-sectionele enquête rapporteerden patiënten consequent baten van CBMs op meerdere domeinen waarvan bekend is dat ze de kwaliteit van leven bij EB beïnvloeden. Voortbouwend op de bredere CBM-literatuur wordt voorgesteld dat cannabinoïden bij voorkeur affectieve pijnpaden moduleren, wat een mechanistische verklaring biedt voor de klinisch betekenisvolle signalen die werden waargenomen, ondanks het niet behalen van het primaire eindpunt in de C4EB-studie. Belangrijk is dat de C4EB-studie wordt beschouwd als informatief in plaats van louter negatief: het biedt proof-of-concept voor een gecontroleerd studieontwerp bij EB, genereert de eerste gecontroleerde veiligheidsgegevens voor sublinguale CBMs in deze populatie, en demonstreert voor het eerst dat patiënten met EB veilig resting-state fMRI kunnen ondergaan in een studiesetting. Tijdige nociceptieve pijncontrole kan ook helpen nociplastische transitie te voorkomen, waardoor effectieve analgesie in een vroeg stadium wordt gepositioneerd als een potentieel ziektemodificerende strategie.

CONCLUSIE

Pijn bij EB is ernstig, multidimensioneel en onvoldoende behandeld. Dit proefschrift brengt de breedte van de last in kaart en richt zich op affectieve en nociplastische dimensies die nociceptie-gerichte behandelingen niet volledig kunnen aanpakken. Hoewel de C4EB-studie haar primaire eindpunt niet haalde, lieten op cannabinoïden gebaseerde geneesmiddelen consistente signalen zien op het gebied van analgesie-sparing, algehele pijnreductie en door patiënten gerapporteerde baten, met een verdraagbaarheidsprofiel dat voortgezette klinische overweging ondersteunt. Wat nu nodig zijn, zijn studies die mechanistisch precies zijn, aangepast aan de beperkingen van zeldzame ziekten en verankerd in uitkomsten die patiënten als betekenisvol ervaren.



Curriculum Vitae



CURRICULUM VITAE

Nicholas Schräder was born on 7 December 1993 in Hong Kong. He completed his International Baccalaureate at Island School, before emigrating in 2012 to Groningen, the Netherlands, to begin his medical education at the University of Groningen.

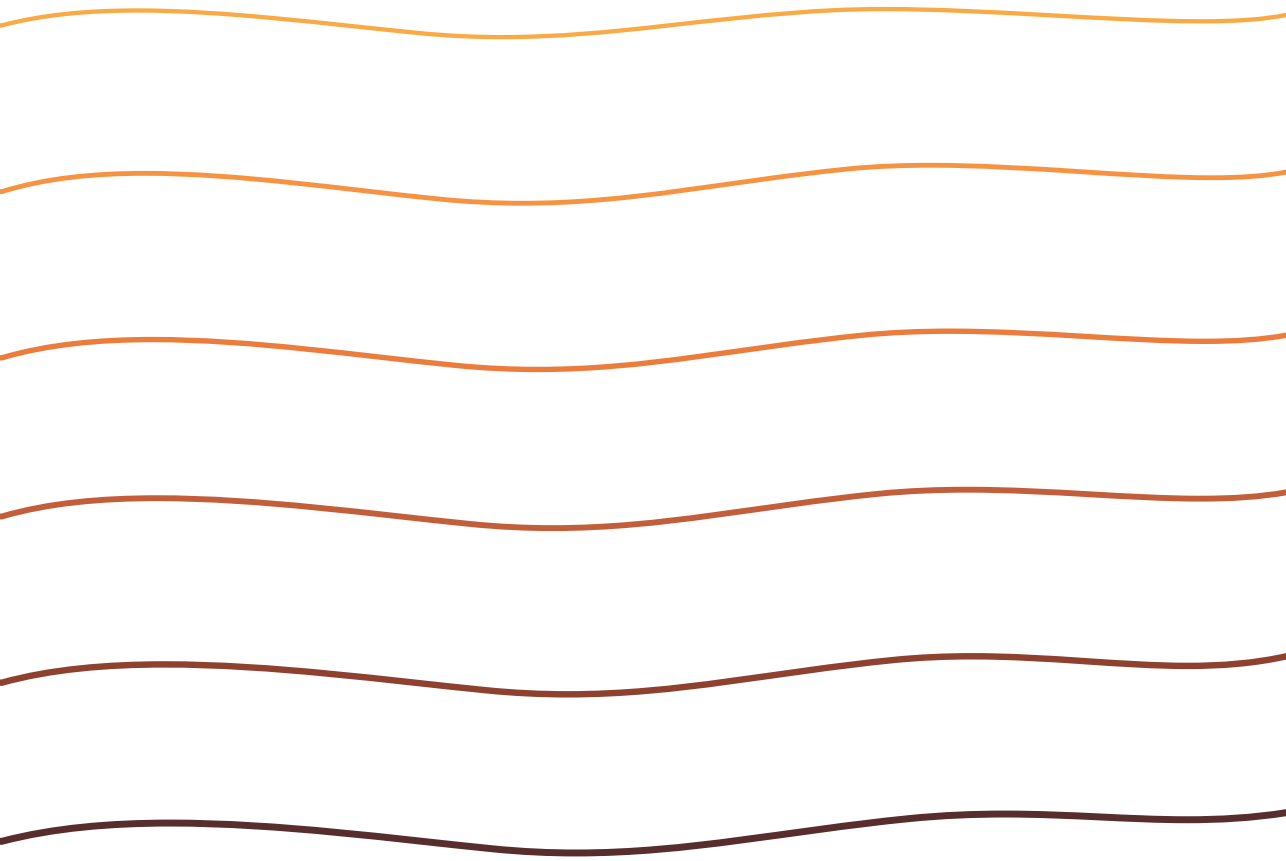
Early on, as a first-year medical student, he became affiliated with the Centre for Blistering Diseases at the Department of Dermatology, UMCG. He spent time on medical internships abroad, both in Hong Kong and Boston, United States. His bachelor thesis was completed at the Great Ormond Street Children's Hospital in London. This research line progressed into an independently funded PhD trajectory after he and Marcel Jonkman received a €176,000 grant from DEBRA UK. Following the sad passing of Marcel Jonkman, André Wolff took over the leadership of the project, and Marieke Bolling onboarded around the same time.

Throughout his research period, he participated in and presented at eight international conferences and several patient symposia. He conducted his research alongside his medical studies and, later, clinical work as a junior doctor (ANIOS). He tutored bachelor medical students and supervised research at two UMCG summer schools for international students.

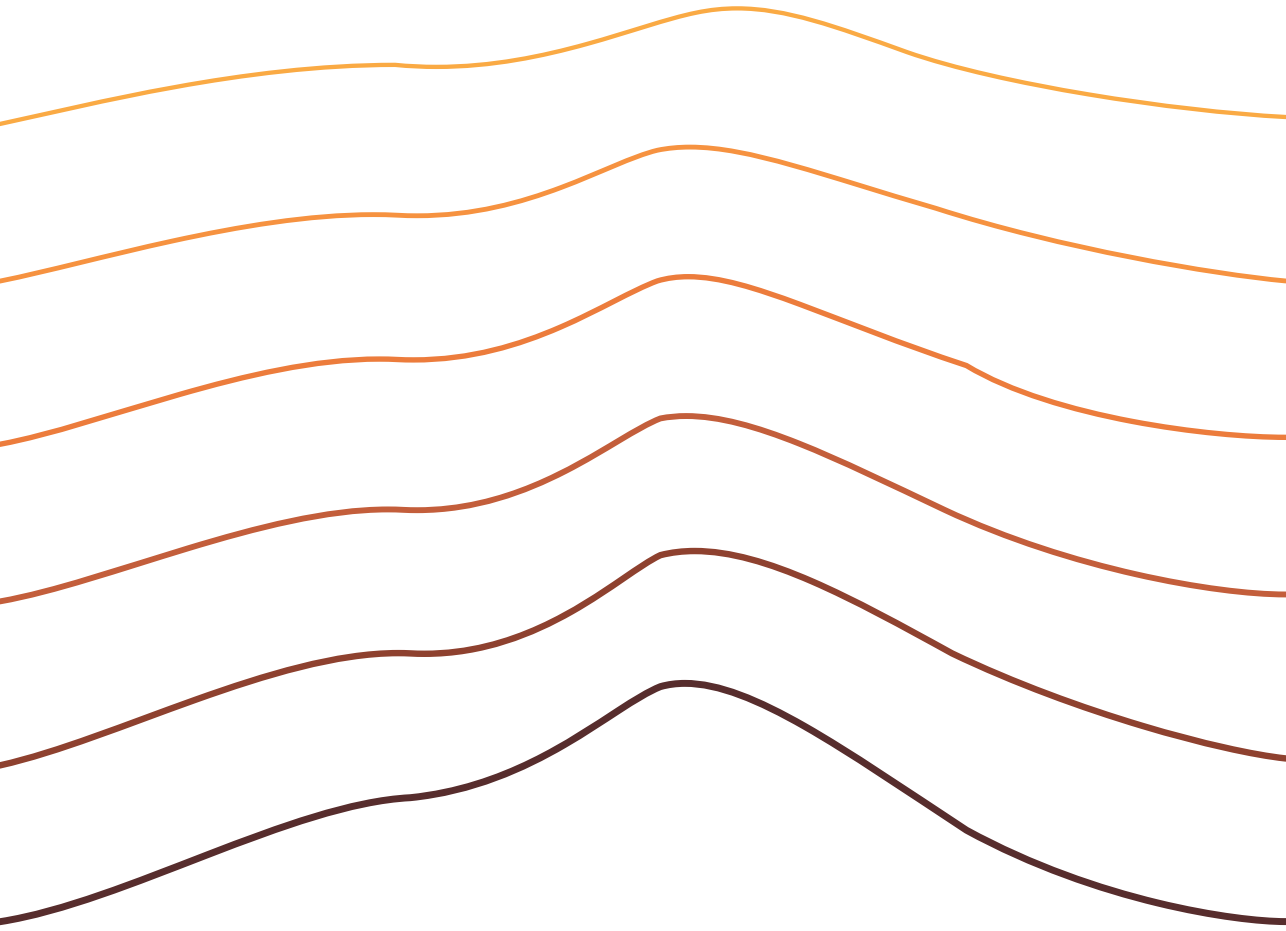
He has a passion for a broad range of clinical specialties, subsequently choosing to pursue general practice. He has been in GP training since 2024 and expects to complete it in the spring of 2027. He will be the fourth-generation general practitioner in his family, following his father, grandfather and great-grandfather.

Other contributions include his board membership of the Dutch Institute of Medical Cannabis and of the charity Running to Stop the Traffik, based in Hong Kong.

In his leisure time, he runs marathons and takes particular joy in ultra-marathons, having completed these in five countries to date.



List of Publications



PUBLICATIONS IN THIS THESIS

1. Schräder NHB, Korte EWH, Duipmans JC, Stewart RE, Bolling MC, Wolff AP. Identifying epidermolysis bullosa patient needs and perceived treatment benefits: an explorative study using the Patient Benefit Index. Journal of Clinical Medicine. 2021;10(24):5836. (Chapter 2)

2. Schräder NHB, Yuen WY, Jonkman MF. Pain Quality Assessment Scale for epidermolysis bullosa. Acta Dermato-Venereologica. 2018;98(3):346–349. (Chapter 3)

3. Schräder NHB, Duipmans JC, Molenbuur B, Wolff AP, Jonkman MF. Combined tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: a report of three cases. British Journal of Dermatology. 2019;180(4):922–924. (Chapter 4)

4. Schräder NHB, Gorell ES, Stewart RE, Duipmans JC, Harris N, Perez VA, Tang JY, Wolff AP, Bolling MC. Cannabinoid use and effects in patients with epidermolysis bullosa: an international cross-sectional survey study. Orphanet Journal of Rare Diseases. 2021;16(1):377. (Chapter 5)

5. Schräder NHB, Duipmans JC, Renken RJ, Sörös P, Vermeulen KM, Bolling MC, Wolff AP. The C4EB study – Transvamix® (10% THC / 5% CBD) to treat chronic pain in epidermolysis bullosa: a protocol for an explorative randomized, placebo controlled, and double blind intervention crossover study. PLoS ONE. 2022;17(12):e0277512. (Chapter 6)

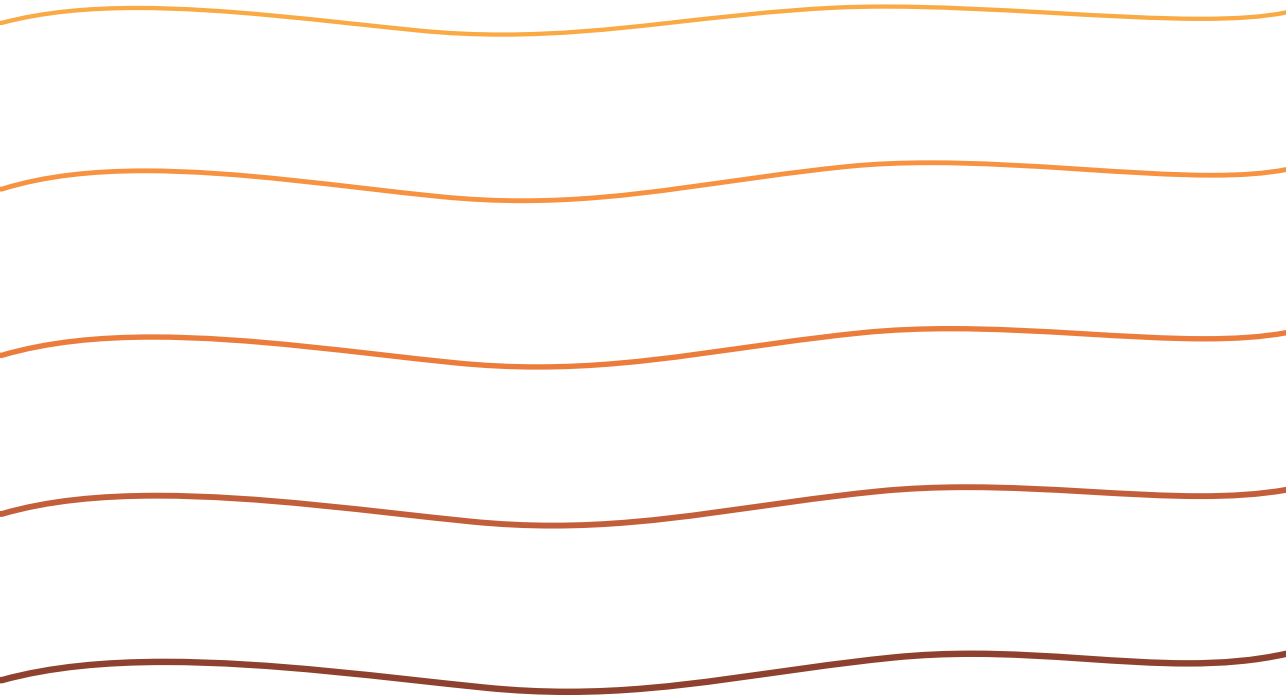
6. Schräder NHB, Duipmans JC, Sörös P, Vermeulen KM, Stewart RE, Bolling MC, Wolff AP. Sublingual tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: a randomized, placebo-controlled crossover study. British Journal of Dermatology. 2026;194(6):1170–1173. (Chapter 7)

7. Schräder NHB, Bolling MC, Sörös P, Vermeulen KM, Stewart RE, Duipmans JC, Wolff AP. Sublingual tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: a randomized, placebo-controlled crossover study – full report with supplementary analyses. Manuscript, unpublished. (Chapter 8)

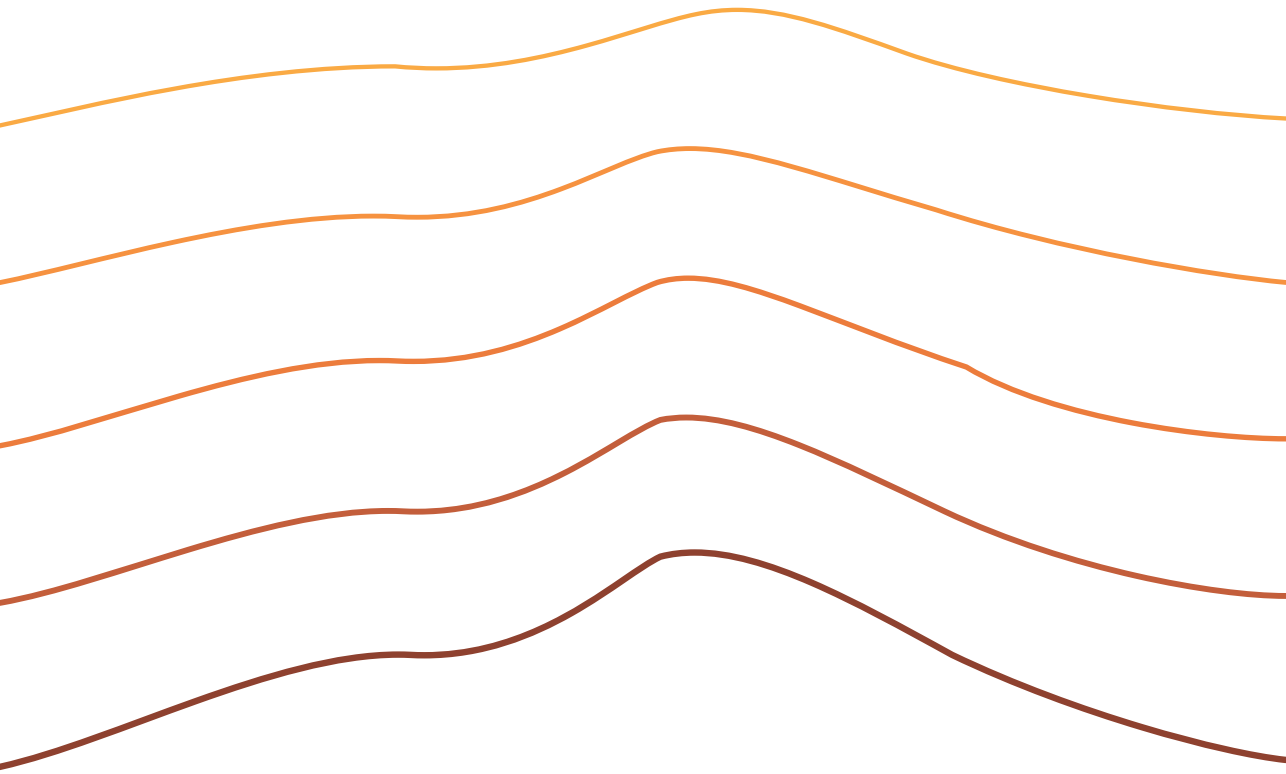
Other publications

8. Schräder NHB, Bolling MC, Wolff AP. Ordering the chaos in cannabinoid-related research: is it time for a task force on taxonomy? Cannabis and Cannabinoid Research. 2021;6(2):174–175.

9. CAIMs Guideline Consortium, incl. Schräder NHB. Clinical practice guideline for the use of complementary, alternative and integrative medicine therapies in epidermolysis bullosa: an international Delphi consensus. British Journal of Dermatology. Submitted.



Acknowledgements



ACKNOWLEDGEMENTS

André Wolff as my promotor, your keen eye for scientific detail, and your coaching on scientific, ethical and even personal matters, shaped much of this thesis. I learned a lot from our, sometimes heated, discussions whether they took place alongside a coffee, or glass of wine. Your work and vision inspired many of my approaches to the projects in this thesis. I wish you a well-deserved relaxing retirement!

Marieke Bolling as my co-promotor you have been a pillar to this project and are exemplary in providing compassionate and high-integrity care to the EB population. You think outside of the box. The medical sciences require a bit of home cooking, Marieke-esque, every now and then, and I'm glad to have shared in some very fun discussions during the EB-CLINET and DEBRA conferences we attended together.

Barbara Horvath, thank you for your role as second promotor and for making the defence possible. You have continued to create an environment that harnesses the potential of the researchers around you.

I would like to thank the reading committee, Prof. Tony Absalom, Prof. Gemma Mellerio and Prof. Paul van Wilgen – much of your work laid the foundations for the scientific journey I embarked upon.

The projects came alive with the input from the many collaborators. My journey began under the mentorship of several colleagues.
Wing Yan, as my master's thesis supervisor, alongside Marcel, you managed to keep me on track, revealing a meaningful publication at the core of this thesis.

Vamsi, like "two-birds" in a cage, for the year we shared a senior-office space. Conversations during our daily walks were inspiring, and I remember when discussing the empirical CBM evidence in our patients, you simply said: "just write it up" – hence, the publication A Report of Three Cases.

José, whom I introduce to others as my second mother. Countless coffees together, drives to EB patient days, fun dinners and gossip. Having only lived in the Netherlands for 2 months, you welcomed me into the EB team at the UMCG and introduced me to your much broader international network. Your office was a place of solace.

Roy and Karin, your patience on this long trajectory, and statistical/ methodological
expertise truly helped make up for my own blind spots, and lack of experience.

Thank you to all the other colleagues who were in many ways involved, from the Department of Dermatology and Anaesthesiology: Rob Spanjersberg, a level-headed and "nuchter" perspective I needed more than once, Albert and Katarina for all the help with logistics and meetings. And a special mention of the derm-lab team, although the work didn't reach the potential I had hoped, I always looked forward to my meditative routine preparing, staining and viewing cannabinoid receptor patterns in the skin, thank you Hendri, Jeroen, Miranda, Marije, Gonnie and Duco.

My paranymphs: Ollie, I'm quite sure we have run over 1500km together in Groningen and several marathons together (Amsterdam, Rotterdam, Leiden and Schoorl). The way you keep your head in the game and get things done is a real talent, and living together was the pinnacle of both of us transitioning from students to working as doctors. Although you can outrun me, I won't forget the time I won 1-on-1 basketball, in the depths of lockdown. Henk Jan, running the bar, Villa Volonté, together reinforced our friendship. You have stayed as far away from research as you could get, but here you will be standing in the Aula. The padel games, and espressos from the at least three "new" coffee machines you've bought were a splendid welcome.

You have both shown integrity and an enjoyment of your respective careers that others aspire to have.
My siblings Chris, Ben and Fleur, I'm not sure you expected to be mentioned, but in many ways your work ethic and commitments to your own field helped to bring this project home.

My parents, Pascale and Hans. You have coached me through all challenges in life, pillars of support. We have had the best of moments, and hardship. We've come out of it. Mum, your undying support for myself, my brothers and sister and those around you deserves a special mention. On behalf of all of us, thank you.

To Lara, my wife, you don't realise the stability and joy you bring. You are a comedian, a chef, a singer, and a perfect distraction to mundane everyday life.

To Marcel Jonkman†, for believing in this project, you were brutally honest, and taught me lessons I will never forget. I'm sorry you couldn't be here.
To my dad, Hans Schräder†, an exemplary general practitioner, my lifelong mentor and a supporting father. Our discussions over the years and shared stories of research and clinical work were often full of humor. I quote "*..sometimes in day to day life you don't see the humor in things...though sometimes you do, when you shouldn't...*"

And most importantly: a thank-you to the wider EB community, patients and families living with EB who participated in this research, who I have met both in and outside of the hospital, at patient gatherings in the Netherlands, Austria, Germany, France, and the UK. You have given me your time and your trust. This
work was inspired by all of you, and we achieved it together.

Men ought to know that from the brain,
and from the brain only, arise our pleasures,
joys, laughter and jests, as well as our
sorrows, pains, griefs and tears.

— Hippocrates of Cos, *The Sacred Disease*