

# Combined tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: a report of three cases\*

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## Summary

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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, they are unable to provide adequate analgesia in a significant proportion of patients. Cannabinoid-based medicines (CBMs) have been studied increasingly for pain conditions of various aetiologies and pose as a novel dimension for pain care in EB. We present three patients with EB who were prescribed pharmaceutical-grade sublingually administered CBMs comprising tetrahydrocannabinol and cannabidiol. All three patients reported improved pain scores, reduced pruritus and reduction in overall analgesic drug intake.

### What's already known about this topic?

- Pain is the most burdening symptom for patients suffering from severe epidermolysis bullosa (EB). Patients are exposed to numerous drug interventions, including high-dose strong opioids, which often do not provide adequate analgesia and may induce adverse effects.
- Cannabinoid-based medicines (CBMs) have been investigated for pain of various aetiologies and show promise through their interaction with the endocannabinoid system localized to central pain circuits.
- Cannabidiol has been reported to reduce wound pain in children with EB.

### What does this study add?

- The prescription of sublingually administered pharmaceutical-grade CBMs may add additional value to pain-care in EB and should be further investigated.

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,<sup>1</sup> and leads to significant distress and poor quality of life.<sup>2</sup> The challenging management of pain in EB is characterized by a noteworthy consumption of pain medication. Opioids underpin EB pain care starting as early as infancy; however, they are considered problematic due to developing tolerance, dependence, opioid-induced hyperalgesia, hormonal changes and obstipation. This concerns both patients with EB and caregivers, and urges a pursuit for alternative treatments.

In the Netherlands, the prescription of pharmaceutical-grade cannabinoid-based medicines (CBMs) containing tetrahydro-

cannabinol (THC) and cannabidiol (CBD) for pain has continually increased since becoming medically available in 2003.<sup>3</sup> The use of CBMs for pain in EB is discussed increasingly,<sup>4</sup> yet remains unexplored territory. Here we report anecdotal outcomes of three patients with EB suffering from refractory pain who were prescribed CBMs.

## Case report

### Case 1

A 64-year-old woman (EB012-01) diagnosed with junctional EB generalized intermediate (JEB-gen intermed) suffered from refractory pain for over 20 years, reporting 9/10 for pain on the visual analogue scale (VAS). Her daily pain therapy included 3 ×

1000 mg paracetamol, 2 × 10 mg oxycodone extended release (ER), 1 × 10 mg codeine-phosphate, 2 × 25 mg amitriptyline and 1 × 5 mg g<sup>-1</sup> topical morphine (applied to the painful right heel). However, this regimen could not provide satisfactory analgesia. Ten years prior, she attempted treatment with an inhaled CBM; however, she experienced only short-lived analgesia (< 45 min), and the presence of euphoria and dizziness. Subsequently an orally administered CBM tea was prescribed with no adequate pain relief.

Sublingual CBM oil (20 mg mL<sup>-1</sup> CBD, 13 mg mL<sup>-1</sup> THC) was started at 0.5 mg CBD and 0.325 mg THC, 4 × daily and increased stepwise up to 2.5 mg CBD and 1.625 mg THC, 4 × daily. She reported VAS scores ranging between 1/10 and 4/10. At 3 months, she was weaned off oxycodone-ER and at 6 months, oxycodone immediate-release (IR) was used for dressing changes only. During the following 2 years, treatment with topical morphine was replaced with 1 mg CBD and 0.65 mg 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 man (EB132-01) diagnosed with JEB-gen intermed was treated for pain, for over 10 years, with 1000 mg paracetamol, 4 × 200 mg ibuprofen, 20 mg oxycodone-IR and 5 mg g<sup>-1</sup> 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 (20 mg mL<sup>-1</sup> CBD, 13 mg mL<sup>-1</sup> THC). At 1 month he reached a dose of 3 mg CBD and 1.95 mg THC, 4 × 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 6 months, due to an increase of wound pain, supplementary treatment was started with 5 mg oxycodone-IR 3 × 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 was maintained. He stopped CBM treatment 2 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 15 mg daily for 2 weeks, which provided only moderate analgesia. His pain treatment remains unresolved.

### Case 3

A 36-year-old man (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 oxycodone-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 6 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 to side-effects, a sublingual CBM oil (20 mg mL<sup>-1</sup> CBD, 13 mg mL<sup>-1</sup> THC) was started. At 1 week he reported a 40% reduction in pain intensity. Both the sublingual CBM and intrapulmonary CBM were continued for 2 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 sequela of metastasized cutaneous SCC and persisted to continue both intrapulmonary and sublingual CBM administration, combined with 10 mg amitriptyline and 10 mg prednisolone, daily. He died at 38 years of age.

## Discussion

Pain in EB significantly impacts quality of life and day-to-day functioning.<sup>1,5</sup> In addition to nociceptive pain associated with blistering and wounds, peripheral nerve damage objectified in RDEB,<sup>6</sup> and postulated in JEB, adds plausibility to reported high pain scores in these EB types.<sup>7</sup> 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.<sup>8</sup>

The persistent inflammatory condition in RDEB skin may also contribute to central sensitization to painful stimuli,<sup>6</sup> which is challenging to objectify through diagnostic techniques, and does not respond adequately to targeted therapies.<sup>9</sup> The different aetiologies of pain in EB require tailored interventions and therefore pain care is optimized through combined drug treatments and psychological 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 aetiologies.

All three patients were prescribed CBMs, comprising THC and CBD, by way of sublingual administration, with good effects. However, two patients 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.<sup>10</sup> 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.<sup>11</sup>

Cannabinoids mimic the actions of endocannabinoids, endogenous ligands, which play a key role in synaptic transmission. Pain modulation has been a central point of discussion, explained, among other reasons, by the actions of cannabinoids on neuronal circuits through cannabinoid-binding receptor (CB) dependent and independent pathways.<sup>12</sup>

CB1 and CB2 are expressed on presynaptic terminals of primary afferent pain circuits, brain areas processing nociception, including the central–medial thalamic nuclei, periaqueductal grey and raphe nuclei, and are colocalized with  $\mu$ -opioid receptors in the spinal cord junction for peripheral nociceptive neurons. The role of CB2 antinociception 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.<sup>13</sup> 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.<sup>13</sup>

Pruritus entails the largest physical and psychological burden for children with EB,<sup>2</sup> and the reported diminished frequency and intensities of pruritus in these cases is notable as the antipruritic effects of CBMs have been postulated in several dermatological conditions.<sup>14</sup>

In these cases, patients were prescribed a 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.<sup>15</sup> CBD, in contrast to THC, has a low affinity for CB1/2, and at high doses does not produce psychotropic effects.<sup>13</sup> Interestingly, CBD is able to antagonize undesired effects of THC such as sedation and intoxication while concurrently improving desirable effects like analgesia.<sup>13</sup>

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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