EPIDERMOLYSIS BULLOSA

CHI Formulary Development Project

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Table of Contents

Related Documents

Related SOPs

· IDF-FR-P-02-01-IndicationsReview&IDFUpdates

· IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

· IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

B-VEC	Beremagene Geperpavec
CBPG	Cord Blood Platelet Gel
CBT	Cognitive Behavioral Therapies
CHI	Council of Health Insurance
CI	Confidence Interval
CPG	Clinical Practice Guideline
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic EB
DEBRA	Dystrophic Epidermolysis Bullosa Research Association
EB	Epidermolysis Bullosa
EBS	EB Simplex
ERN- Skin	European Reference Network for Rare and Undiagnosed Skin Diseases
FDA	Food and Drug Administration
IDF	Insurance Drug Formulary
JEB	Junctional EB
KEB	Kindler EB
LLLT	Low-Level Laser Therapy
RDEB	Recessive dystrophic epidermolysis bullosa
SCC	Squamous Cell Carcinoma
SFDA	Saudi Food and Drug Authority

Executive Summary

Inherited epidermolysis bullosa (EB) represents a group of genetic conditions characterized by skin and mucous membrane fragility, resulting in blistering.[1]

Wounds and related care are the most important sources of pain in EB patients. The intensity of pain is frequently related to disease severity and extent and affects the quality of life of patients and family members. Itch is also a common and disabling symptom in all EB forms.

There are four main types of EB:

- EB simplex (EBS): Manifests as superficial, erosive, and crusty lesions. Healing occurs without scarring, but pigmentary changes may occur. Chronic wounds are not typical.
- Junctional EB (JEB): Characterized by chronic wounds with exuberant granulation tissue, often affecting the face, occipital area, diaper area, and extremities. Healing can result in pigmentary changes or scarring.
- Dystrophic EB (DEB): Wounds heal with scarring and milia formation. Recurrent wounds may appear in areas exposed to trauma, and over time, they can become chronic.
- Kindler EB (KEB): Presents with erosions and crusts in childhood. As the tendency for blistering decreases with age, wounds become rare.

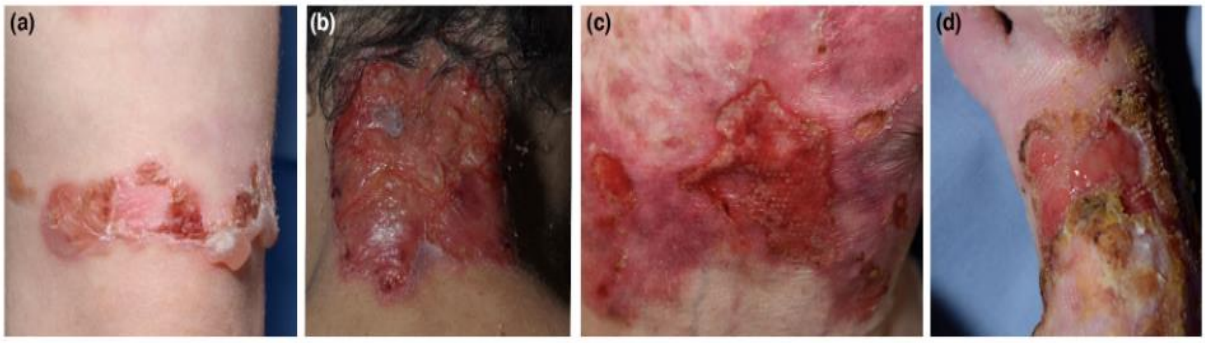

Figure 1. *Variable wound characteristics in epidermolysis bullosa (EB). (a) Erosions with crusts in EB simplex, (b) chronic wound in junctional EB, (c) wound on scars in recessive dystrophic EB (RDEB), (d) squamous cell carcinoma (SCC) in severe RDEB*

The main EB subtypes of EB:

- EBS severe
- EBS intermediate or localized
- EBS with muscular dystrophy

- JEB intermediate
- JEB XVII collagen deficiency
- JEB with integrin deficiency
- Recessive dystrophic severe EB
- Dominant DEB

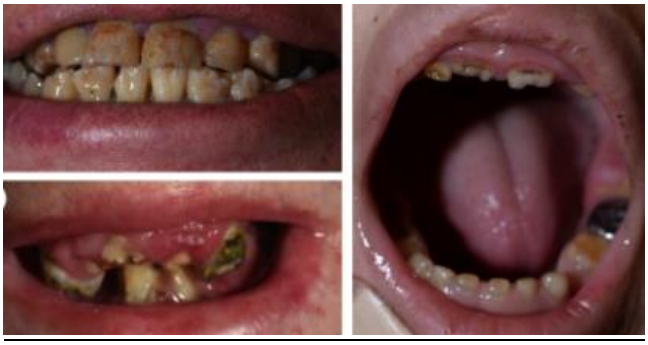

Figure 2. *Oral manifestations of epidermolysis bullosa (EB)*

Symptoms and complications depend on the type of EB but can include hoarse cry, cough, alopecia, blistering (erosion of the skin) and skin fragility around the eyes and nose, blistering in or around the mouth and throat causing feeding or swallowing difficulty, dental abnormalities such as tooth decay, nail loss or deformed nails, scarring and malnutrition.

The exact prevalence of EB is unknown. Worldwide, an estimated 50 in 1 million live births are diagnosed with EB, and 9 in 1 million are in population. Of these cases, approximately 92% are EBS, 5% are DEB, 1% is JEB, and 2% are unclassified.[2]

The prevalence of EB in Middle Eastern countries, including Saudi Arabia, has not been extensively studied in terms of epidemiological figures and clinical patterns. To address this gap, a retrospective study was conducted in the Eastern province of Saudi Arabia to establish the prevalence of EB and to demonstrate the efficacy of pharmacological management (phenytoin) and good nutrition in the treatment of EB (section 1.1.1).[3]

Non-pharmacological treatment strategies for EB center around meticulous wound care and preventive measures to enhance the well-being of affected individuals. Wound dressing, incorporating non-adherent materials, is essential for protecting and promoting healing. Antiseptic techniques and regular cleaning help prevent infections, a common concern due to compromised skin integrity. Nutritional support involves maintaining a well-balanced diet and addressing potential deficiencies with supplements. Physical therapy, including a range of motion exercises and adaptive devices, aids in maintaining joint mobility and preventing contractures. Psychosocial support through counseling and education plays a vital

role in coping with the challenges of EB. Protective measures, including the use of soft clothing and avoidance of irritants, mitigate trauma to the skin. This multidisciplinary approach aims to optimize the quality of life for individuals living with EB.

The pharmacological treatment of EB primarily involves managing symptoms and preventing complications more than directly addressing the disease itself. The approach to treatment often varies based on the type and severity of EB. Emphasizing symptomatic relief, the use of non-opioid analgesics (such as acetaminophen and ibuprofen), opioid analgesics (including tramadol, codeine, and morphine), and gabapentin aims to alleviate pain associated with blistering and wound care. Topical antibiotics like fusidic acid play a crucial role in both preventing and treating infections. Itch control is addressed with antihistamines like diphenhydramine, while nutritional supplements may be recommended to combat malnutrition, especially in severe cases. The evolving field of EB research explores experimental therapies, such as gene therapy and protein replacement, offering hope for more targeted treatments in the future.

This report compiles all clinical and economic evidence related to EB according to the relevant sources. The ultimate objective of issuing EB guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to IHs patients in Saudi Arabia. The focus of the review was on Saudi, American, European, and international guidelines issued within the last ten years.

This indication report does not cover the management of epidermolysis bullosa acquisita (EBA), a distinct acquired autoimmune subepidermal blistering disease, which falls under pemphigoid diseases.

Several classes and drugs can be used for the management of EB and are summarized in the table below.

Table 1. SFDA-Registered Drugs for the Management of Epidermolysis Bullosa

Drug	Indication	Dose	HTA recommendation
NON-OPIOID ANALGESICS			
Acetaminophen	Alone or with an anti-inflammatory, for the management of mild pain associated with blistering and wounds.	1g every 6hours	No HTA recommendations.
Ibuprofen	Alone or with acetaminophen, for the management of mild pain and reduce inflammation associated with blistering and wounds.	200 to 400 mg every 4 to 6 hours as needed or 600 to 800 mg every 6 to 8 hours as needed.	No HTA recommendations.
ANTIEPILEPTICS			
Gabapentin	Management of chronic neuropathic pain associated with blistering and wounds and for itching.	100 to 300mg, 1 to 3 times daily. Target dose: 300 mg to 1.2 g 3 times daily.	NICE: positive recommendations.
OPIOID ANALGESICS			
Morphine	Management of severe, neuropathic, and chronic pain associated with blistering and wounds.	Oral: 5 to 15 mg every 4 hours as needed. IV: 1 to 4mg every 1 to 4h as needed.	HAS: positive recommendations.

Tramadol	Tramadol may be considered for acute rescue therapy in moderate pain.	25 to 50mg every 6h (max 400mg per day).	NICE: positive recommendations.
TOPICAL ANTIBIOTICS			
Fusidic acid (topical)	Topical treatment of wound infections in EB patients.	Two to three times daily.	No HTA recommendations.
NMDA RECEPTOR ANTAGONISTS			
Ketamine	Management of severe, refractory and chronic pain associated with blistering and wounds.	PO: 0.5 mg/kg/day administered in 3 to 4 divided doses as needed; then increase dose in increments of ~5 mg/dose based on pain goal and tolerability; maximum daily escalation dose. IV: 0.05 to 0.15mg/kg/h. SUBQ: 0.1 to 0.6mg/kg as needed.	NICE and CADTH: positive recommendations.
TRICYCLIC ANTIDEPRESSANT			
Amitriptyline (Not SFDA-registered, available through special import)	Management of chronic neuropathic pain associated with blistering and wounds and for itching	Initial dose: 10 to 25mg per day. Target dose: 25 to 125mg per day.	NICE: positive recommendations.

Non-SFDA registered drugs

Recent research has paved the way for numerous potential treatments in EB, many of which are in various stages of clinical trials, encompassing topical, oral, and injection modalities:

- The FDA's May 2023 approval of **beremagene geperpavec** (B-VEC) for DEB treatment, a non-invasive topical gene therapy, is a notable breakthrough. The GEM-3 trial is a phase 3, double-blind, intrapatient randomized, placebo-controlled trial involving patients 6 months of age or older with genetically confirmed DEB. For each patient, a primary wound pair was selected, with the wounds matched according to size, region, and appearance. The wounds within each pair were randomly assigned in a 1:1 ratio to receive weekly application of either B-VEC or placebo for 26 weeks. At 6 months, complete wound healing occurred in 67% of the wounds exposed to B-VEC as compared with 22% of those exposed to placebo (95% confidence interval [CI], 24 to 68; P=0.002). Pruritus and mild systemic side effects were observed in patients treated with B-VEC.[4]
- Oleogel-S10 (birch triterpenes), approved in Europe for EB, showing efficacy in JEB and DEB patients. Results from the phase III randomized double-blind phase of the EASE study were published in January 2023, in which a total of 223 patients with DEB, JEB, and KED were enrolled to receive at a 1:1 ratio Oleogel-S10 or control gel. Oleogel-S10 resulted in 41.3% of patients with first complete target wound closure within 45 days, compared with 28.9% in the control gel arm (relative risk 1.44, 95% CI 1.01-2.05; P = 0.013). Adverse events (AEs) occurred with similar frequency for Oleogel-S10 (81.7%) compared with control gel (80·7%).[5]

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of EB, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, no clinical guidelines for the management of EB have been published by Saudi bodies. A 1993 study looking at the epidemiology of EB in the Kingdom of Saudi Arabia was published in the International Journal of Dermatology.

1.1.1 Epidermolysis Bullosa in the Eastern Province of Saudi Arabia (1993)

To determine the prevalence of EB in the Eastern Province of Saudi Arabia, a retrospective review of 49,902 cases seen at our referral clinic from 1984 through 1990 was conducted. Among these cases, we identified sixteen instances of EB.[3]

Pattern of cases of EB

Among 16 cases of EB, 10 (62.5%) had recessive dystrophic epidermolysis bullosa (RDEB), four (25%) had epidermolysis bullosa simplex (EBS), one had dominant dystrophic epidermolysis bullosa (DDEB), and one presented with recurrent bullous eruptions of the hands and feet (Weber-Cockayne syndrome). Most of the cases, specifically twelve (75%), fell within the age group of 0 to 10 years. Notably, 87.5% of the parents in the 16 cases had consanguineous marriages, predominantly among cousins.

Genetic pattern and family history

The consanguinity rate in this small group is notable, with 87.5% of cases having a familial connection. Autosomal dominant inheritance was observed in cases of EBS, DDEB, and Weber-Cockayne syndrome. RDEB followed autosomal recessive inheritance.

Management of EB

In a therapeutic trial, oral phenytoin was administered to three severe cases of RDEB, and their progress was compared with that of three less severe cases of RDEB.

In the absence of specific measures to control basal cell proteolysis, collagen degeneration, necrosis, and intramembrane defects leading to bulla formation in EB, therapeutic interventions focused on palliative and supportive measures to enhance life expectancy. Upon clinical diagnosis and histological confirmation, hospitalized

patients received meticulous nursing care to minimize trauma and relieve pressure on affected areas:

- Saline soaks and cool compresses were utilized to reduce friction and remove debris from eroded skin and mucosa.
- Topical and systemic antibiotics were employed to manage bacterial infections. Nutritional support included blended semi-solid foods and protein and vitamin supplements.
- A therapeutic trial with oral phenytoin was conducted in three severe cases of RDEB, introducing a regimen initiated by Bauer et al. The trial resulted in a marked reduction in blister count within two weeks, with sustained improvement observed for over a year in two patients continuing the trial after one patient's unfortunate died in infancy due to bacterial septicemia. The progress was notably more significant in these two cases than in milder cases not on the drug, and no adverse effects of phenytoin were reported or observed.

1.2 European Guidelines

1.2.1 Practical Management of Epidermolysis Bullosa: Consensus Clinical Position Statement from the European Reference Network for Rare Skin Diseases (2021)

A position paper published in 2021 by the European Reference Network for Rare and Undiagnosed Skin Diseases (ERN-Skin) provides practical consensus recommendations for managing patients with Epidermolysis Bullosa (EB), covering various aspects such as diagnosis, wound management, oral care, and treatment of pain and itch.[6]

Diagnosis of EB

Providing a precise diagnosis stands as the initial phase in addressing a patient suspected of having EB and offers crucial prognostic insights. The diagnosis involves a comprehensive assessment of clinical features, family history, and laboratory findings.

- **Clinical manifestations of EB** include recurrent blisters and erosions of the skin and/or oral mucosa, present since birth or emerging later in life, triggered by mild physical trauma, and resulting in congenital skin loss. The differential diagnoses vary across age groups. In neonates, consider infections and genetic disorders; in infancy and childhood, evaluate for bullous mastocytosis, genetic disorders, and autoimmune blistering disorders; in adults, explore causes such as infections, adverse drug reactions, autoimmune blistering disorders, and dermatitis artefacta.

- **Specific tests for EB laboratory diagnosis**: genetic testing is considered the gold standard for providing a definitive diagnosis and classifying major EB types and subtypes. Immunofluorescence mapping or immunohistochemistry offers a rapid diagnosis, especially valuable for newborns, aiding prognosis determination. These methods can diagnose severe EB subtypes based on skin cleavage level and specific protein absence or reduction. However, in cases with mild skin fragility, Immunofluorescence mapping and Transmission Electron Microscopy may not be conclusive. Transmission electron microscopy is essential for determining skin cleavage level and anomalies in keratin intermediate filaments, hemidesmosomes, basement membrane, or anchoring fibrils, aiding in the early diagnosis of certain EB subtypes, such as dominant EBS severe.

Wound management

Wound care is the cornerstone of treatment for patients with EB and should take into consideration the subtype of EB, the patient's age, factors such as nutritional status (chronic anemia and hypoalbuminemia), the characteristics of the wound (erosive and scarring), associated symptoms (pain and itch), any restrictions on the patient's daily activities, and the patient's adherence to treatment.

- Wounds should be cleaned with low-toxicity solutions (saline, polyhexanide, sodium hypochlorite 5–10 mL in 5 L water, acetic acid ≤ 0.25%, chlorhexidine 0.1%).
- Gentle debridement of crusts and slough should be regularly performed by soaking and bathing in order to accelerate the healing process.
- A variety of specialized dressings are employed based on the specific type of wound. These dressings include non-adherent contact layer dressings, foam dressings, hydrogel dressings, hydrofiber dressings, alginate dressings, and antimicrobial dressings. Each type of dressing serves a unique purpose in managing different aspects of wound healing and addressing the challenges posed by EB, such as the fragility of the skin and the risk of infection.
- For critically colonized wounds, a lipid-stabilized hydrogen peroxide cream, applied directly or on a contact dressing, can effectively reduce bacterial load after mild antiseptic cleaning.
- Infected wounds require daily dressing changes, using the same options as for heavily exudative wounds. Principles for administering topical antibiotics/antimicrobials include restricting use to critically colonized and infected wounds, preferring agents without systemic formulations (e.g., fusidic acid), limiting application time to prevent resistance, and considering retapamulin 1% ointment for resistant Gram-positive bacteria.

- Implement routine measures such as padding trauma-exposed areas, choosing suitable footwear, using appropriate hosiery, and avoiding tight clothing.
- Optimize nutrition for wound healing and maintain hemoglobin levels for chronic anemia.

The healing of chronic wounds should be diligently monitored. Typically, a reduction in wound size by 20–40% within 2–4 weeks is considered a reliable indicator for predicting complete healing by week 12. Additionally, other parameters, such as diminished pain and itch, along with the resolution of any infection, should be assessed during the monitoring process.

Oral health care in EB

Oral health is a major aspect of EB management, being crucial for appropriate feeding and speech and impacting on wound healing and growth. Patients with JEB, RDEB and KEB experience the most severe oral problems.

Preventing and managing oral manifestations in individuals with EB involves early dental referral, education, and tailored preventive measures. Oral hygiene routines should be personalized, emphasizing gentle techniques, fluoride application, and daily cleaning of interdental spaces. Antiseptic mouthwashes and regular dental care are recommended.

Treatment strategies consider the patient's mucosal fragility, employing careful handling and protective measures during dental procedures. Sealing caries-free surfaces and considering dental interventions like crowns or implants are adapted to the individual's needs. In severe cases, early molar extraction and antibiotic treatment during oral surgery may be considered to prevent complications. Moisturizing and protecting lips, along with a soft food diet, contribute to overall oral health in individuals with EB.

Management of pain

Wounds in individuals with EB lead to severe pain, a debilitating symptom significantly impacting quality of life. While pain is prevalent in both adults and children with EB, its management varies.

Pain can be categorized into three types: nociceptive pain, neuropathic pain, and psychogenic pain. Nociceptive pain originates from injury or damage to a part of the body, excluding nerve tissue, activating specialized nerve endings at the affected site. Neuropathic pain results from issues within the nervous system, stemming from injury or disease to the nerve tissue. Neuropathic pain is often more challenging to treat compared to nociceptive pain.

The challenge lies in effectively controlling pain, especially during dressing changes, a crucial aspect for patients.

Table 2. Pain Management in Epidermolysis Bullosa

Pain Management Approach	Examples of Medications/Strategies
Mild Pain	**Non opioid analgesics:** - Acetaminophen: 15mg/kg/6h PO - Ibuprofen: 7–10 mg/kg/6 h PO, max. 30 mg/kg/day
Moderate Pain	**Opioids analgesics:** - Tramadol: 0.5–2 mg/kg/6 h PO
Severe Pain	**Morphine:** • <6 months: 25µg/kg/h or 0.1 mg/kg/4 h (oral) or 10–20µg/kg/h (IV). • 6 months–5 years: 50µg/kg/h or 0.2 mg/kg/4 h (oral) or 25–50µg/kg/h (IV). • 6–12 years: 50µg/kg/h or 0.2 mg/kg/4 h (oral) or 25–50µg/kg/h (IV). • 12–15 years and>35 kg:5 mg every 4 h (oral) or 0.5 mg/h (IV). • >15 years and>40 kg: 5 mg every 4 h (oral) or 1 mg/h (IV).
Chronic Pain Management	**Gabapentin**: start at 5 mg/kg/day in 3 oral doses then gradually increase (every5 days) depending on effectiveness up to 10–30 mg/kg/day.

1.3 International Guidelines

1.3.1 International Guidelines Clinical Practice Guidelines: Oral Health Care for Children and Adults Living with Epidermolysis Bullosa (2020)

Inherited EB is a genetic disorder characterized by skin fragility. Individuals affected by this condition exhibit distinctive oral features, necessitating a specialized approach from dental teams. The International Dystrophic Epidermolysis Bullosa Research Association (DEBRA International) serves as the global network of national groups dedicated to supporting those impacted by EB. As part of their commitment to ensuring access to the highest quality support and medical care for individuals with EB, DEBRA International entrusts the development of Clinical Practice

Guidelines (CPG) to healthcare professionals with significant expertise in EB globally. The initial CPG on oral health care for EB patients was published in 2012. Since then, new literature reviews, case series, and case reports have emerged, highlighting the need to update the guidelines with the latest evidence and involve experts from various centers worldwide. External specialists and healthcare professionals from a multidisciplinary team as well as patients and representatives from DEBRA association groups in Australia, Brazil, New Zealand, Spain, and the United States reviewed the consensus report.[7]

Oral manifestations of EB exhibit varying frequency and severity based on the disease subtype. Most patients typically display vesiculobullous oral lesions, ranging from small, discrete vesicles to large bullae and areas of granulation tissue. These lesions can be found on all mucosal surfaces, with the most severe impact observed in patients with generalized RDEB. The involvement of dental hard tissues is contingent on the specific form of EB. Individuals with JEB commonly exhibit generalized enamel hypoplasia, while those with RDEB experience a notably higher incidence of caries compared to other EB types or unaffected controls. On the other hand, individuals affected by Kindler EB are more prone to periodontal disease. An early study involving 101 individuals with EB revealed that oral blisters were present in 97% of RDEB patients, 45% in DDEB, 37% in JEB, and 38% in EBS. Additional features such as microstomia were noted in 54% of RDEB cases, 7% of JEB cases, and were absent in patients with DDEB and EBS. Therefore, thorough comprehension of these subtypes is crucial for clinicians in strategizing comprehensive care, both in the initial stages and for long-term management. Given the rarity of the disorder and the presence of multiple comorbidities, it is imperative to adopt a multidisciplinary care approach for individuals with EB.

The method used for formulating the recommendations, including the levels of evidence and the grades of recommendations, can be found in appendix B.

Early referral (good practice point): Dental care constitutes an integral part of the multidisciplinary team for individuals with EB. As such, patients should be promptly referred to a dentist upon diagnosis. Ideally, this referral should occur before any oral issues manifest, preferably within the first 3 to 6 months after diagnosis. During the initial consultation, the following objectives should be addressed:

1. Education of parents and caregivers: This involves providing guidance on various aspects such as diet (including sugar-free medications), oral hygiene routines, the use of fluorides, technical aids, and an understanding of the oral manifestations associated with EB. Importantly, this preventive advice should be offered even before the eruption of the teeth.
2. Early diagnosis of enamel abnormalities such as those seen in JEB. This is possible as soon as the first primary tooth erupts.

3. Early diagnosis of tooth crowding, mainly in RDEB.
4. Early diagnosis of incipient caries lesions.

Oral bullae and ulcerations: While oral bullae, ulcers, and erosions represent the predominant oral features in individuals with EB, only two published studies have explored therapeutic approaches for these oral lesions. In 2001, Marini and Vecchiet reported that sucralfate suspension effectively reduced the development and duration of oral mucosal blisters and ulcers, alleviated associated oral pain, and improved plaque and gingival inflammation indices. Similarly, Sindici and colleagues conducted a pilot evaluation in 2017, assessing the use of Cord Blood Platelet Gel (CBPG) and Low-Level Laser Therapy (LLLT) over a 3-day treatment period. This involved daily applications on 19 long-standing symptomatic oral lesions in seven patients with DEB. Results indicated improved reported pain and clinical lesion size from the first day of treatment, reducing discomfort from ulceration. During the follow-up period, only one patient developed a new lesion in the same treatment site, while all patients retained other oral lesions at untreated sites. The sole reported adverse effect was the lingering unpleasant taste of the medication, reported by two patients (28%) after 24 weeks.

In addition to these strategies, mouthwashes and oral gels designed to manage mucositis and oral lesions are commonly prescribed to individuals with EB. Products such as Gelclair® (Helsinn Healthcare SA, Switzerland), K-trix® (calendula-based; Farpag, Colombia), and Dentoxol® (Ingalfarma, Chile) are among those available. Some patients also opt for gargling saltwater as a cost-effective and readily available alternative, although there is a lack of published scientific reports on its effectiveness in EB.

Oral hygiene (D):

- Chlorhexidine 0.12% is frequently recommended for preventing oral diseases in individuals with EB. Its effectiveness has been demonstrated against candida, although it has proven ineffective for controlling caries. Various application methods, such as mouthwashes, swabs, sprays, gels, and topical varnish applications, have been employed. A sample preventive treatment protocol involves rinsing twice a day for two weeks every three months.
- Alcohol-free formulations are advised in patients with oral lesions: It is recommended to use formulations without alcohol in patients with oral lesions.
- For dental care in children, caregivers are advised to initiate tooth brushing as soon as the child's teeth emerge. The use of fluoridated toothpaste is recommended, with an appropriate dosage based on the child's age. Topical applications of high-dose fluoride varnish are recommended every 3 months

for individuals with a high risk of caries or at each dental visit. Fluoride can be administered in various forms, including foam, gel preparation, or mouthwash. Gel preparations can be applied using a toothbrush, a custom-made plastic tray, or with the use of cotton rolls.

Dietary adjustments

The nutritional needs of individuals with EB, especially in severe subtypes like RDEB, can be substantially elevated. A consistent and targeted intake of high-calorie and high-protein foods is crucial for growth and to prevent comorbidities related to malnutrition. To meet these elevated targets, dietary guidance may include the use of high-sucrose nutritional supplements, which can be particularly cariogenic. Leal and colleagues discovered that patients with RDEB exhibit a similar frequency of food intake and sugar content as the control group, with the primary distinction being the consistency of food. Patients with DEB tend to prefer soft food.

1.3.2 Pain Care for Patients with Epidermolysis Bullosa: Best Care Practice Guidelines (2014)

EB has multi-system effects and patients present with a number of both acute and chronic pain care needs. Effects on quality of life are substantial. Due to its low prevalence, expertise in pain care for patients with this disease is often restricted to a few specialized care centers. Even then, evidence-based pain care is limited by a near absence of scientific literature specific to EB. This set of guidelines was requested by Dystrophic Epidermolysis Bullosa Research Association International (DEBRA International) to help standardize the approach to pain care for both adult and pediatric patients with EB in all parts of the world. Consequently, a group of clinical pain care experts from a few countries have come together to lend their experience to the limited scientific literature to create these guidelines. The aim of the guidelines is to provide the user with information on pain care for children and adults with EB. These guidelines can be applied to all patients diagnosed with hereditary forms of EB. Patients with acquired forms are not included in the guidelines.[8]

A. Psychological therapies offer effective approaches to management of chronic and acute pain as well as itching.

- For chronic pain management use CBT. (B)

- For acute pain management, offer the patient distraction, hypnosis, visualization, relaxation, or other forms of CBT. (B)
- Consider habit reversal training, and other psychological techniques for management of pruritus. (C)

B. Postoperative pain can be handled as for other patients in the same setting, with modifications.

- Basic perioperative assessment and pain treatments should be used for non-EB patients, with modification. (A)
- Transmucosal (including intranasal fentanyl and transbuccal opioids) should be considered for short procedures and pain of brief duration when intravenous and enteral routes are unavailable. (B)
- Perioperative opioid use must account for preoperative exposure, with appropriate dose increases to account for tolerance. (B)
- Regional anesthesia is appropriate for pain resulting from major surgeries. Dressing of catheters must be non-adhesive and monitored carefully. (C)

C. Skin wounds and related pain are the hallmark of EB of most subtypes. Prevention and rapid healing of wounds through activity pacing, optimal nutrition and infection control are important. A number of pharmacologic treatments are available.

- Maintain optimal nutrition and mobility and treat infections as indicated. (D)
- Consider topical therapies for pain. (C)
- Systemic pharmacologic therapy should be adapted to treat both acute and chronic forms of skin pain. (B)
- Monitor potential long-term complications of chronically administered medications. (C) (Pediatric)

D. Baths and dressing changes require attention to both pain and anxiety.

- Anxiolytics and analgesics should be used for procedural pain and fear. Care must be taken when combining such medications due to cumulative sedative effects. (B)
- Cognitive behavioral techniques should be implemented as the child becomes old enough to use them effectively. Specifically, distraction should be used for younger children. (B)
- Environmental measures such as adding salt to the water to make it isotonic and keeping the room warm are recommended. (B)

E. EB affects the gastrointestinal tract in its entirety. Pain from ulcerative lesions responds to topical therapy. GERD and esophageal strictures have nutritional as well as comfort implications and should be addressed promptly when found. Maintaining good bowel habits and reducing iatrogenic causes of constipation are crucial.

- Topical treatments are recommended for oral and perianal pain. (C)
- Therapy should be directed to manage gastroesophageal reflux and esophageal strictures using standard treatments. (C)
- Constipation should be addressed nutritionally, with hydration and addition of fiber in the diet to keep stool soft, by minimizing medication-induced dysmotility and with stool softeners. (C)

F. End of Life pain care is an expected part of care for EB, which in many cases is life-limiting in nature. All basic principles of palliative care apply as they do for other terminal disease states.

- Assess and manage physical, emotional, and spiritual suffering of the patient, while providing support for the whole family. (A)
- Opioids are the cornerstone of good analgesia in this setting. Opioid rotation may need to be considered to improve analgesia and reduce side effects, and adjuncts may need to be added. (B)
- Consider targeted medication for neuropathic pain when pain proves refractory to conventional therapies. (D)
- Continuous subcutaneous infusion of combinations of medication is an option when parenteral therapy is needed in the terminal phase. (C)
- Where needed, breakthrough medication can be given transmucosally (oral or nasal) for rapid onset and avoidance of the enteral route. (B)

G. A combination of environmental, cognitive-behavioral, and pharmacologic therapies is available for use for EB-related pruritus, which can be a severe symptom of the disease.

- Use environmental and behavioral interventions for itch control. (C)
- Antihistamines are recommended and can be chosen depending upon desirability of sedating effects. (D)

- Gabapentin, pregabalin, TCA, SNRIs and other non-traditional antipruritics agents should be strongly considered for itch treatment. (C)

H. Recommendations for musculoskeletal pain treatment.

NSAIDs are frequently prescribed to manage bone and joint pain in individuals with various conditions, including EB. While these medications are generally considered suitable, caution is advised due to potential side effects. In such cases, cyclooxygenase-2 inhibitors may offer an alternative with improved tolerance. Acetaminophen is a favorable option for pain control in EB, as it does not impact bleeding. For more intense pain, including joint pain, tramadol and opioids are recommended, and some individuals may opt for long-acting opioid formulations. Joint pain can be addressed through mechanical interventions, physical therapy, CBT, and surgical correction. (C)

I. Recommendations for infant pain care.

For infants with EB, maintaining appropriate moisture levels and promoting wound healing during bathing and dressing changes is crucial. Non-adherent dressings of suitable size are recommended, with increased frequency for infected wounds. Changing dressings one limb at a time is advocated in infants to prevent skin abrasion and the development of painful lesions. This approach also minimizes the risk of bacterial spread from colonized to uncontaminated areas. Adding salt to the bathwater, similar to older patients, is advised.

Infants often require analgesics during these procedures, with NSAIDs, acetaminophen, and opioids being common choices. Codeine is discouraged due to variability in metabolic capacity and responses in neonates. Severely affected hospitalized infants may necessitate extensive pharmacologic support, including around-the-clock or continuous opioid infusion. Gabapentin has shown effective pain control in infants with severe chronic pain, and oral ketamine may be used to supplement opioids during intense dressing changes, although concerns about potential neurodevelopmental effects exist. It's important to monitor opioid-induced constipation and ensure adequate caloric intake for infants on frequent opioid treatment. While ketamine use raises concerns based on animal studies, these effects are not known to occur in human infants, particularly with small, intermittent doses.

J. Recommendations for end-of-life pain treatment.

- Adjunctive measures, such as amitriptyline or gabapentin, have proven effective for neuropathic pain in many EB patients.
- Enteral administration of medications like amitriptyline or gabapentin may take time to achieve their full analgesic effect.

- Ketamine, known for rapid efficacy, can be administered orally or subcutaneously, but bypassing hepatic metabolism may lead to increased sedation and hallucinations.
- In palliative phases or when swift therapy escalation is needed, parenteral administration of analgesia becomes necessary.
- Subcutaneous infusions have been reported to be tolerated in the final days of life in adult EB patients, despite historical concerns about exacerbating blistering. (C)
- Morphine administered subcutaneously has shown efficacy similar to intravenous administration in non-EB patients with cancer pain.
- Transdermal delivery systems are effective but require regular replacement.
- Subcutaneous or intramuscular injections and attempts to obtain intravenous access can be distressing for children with EB.
- Individuals nearing the end of life with EB often require intermittent "breakthrough" doses of analgesia, with recommendations for short-acting opioids at 10-15% of the total background dose from the preceding 24 hours.

1.4 Systematic Reviews/Meta-Analyses

A thorough search of database yielded no results in terms of systematic reviews and meta-analyses covering the management of epidermolysis bullosa.

Section 2.0 Drug Therapy

2.1 Nonopioid Analgesics

2.1.1 Acetaminophen

Information on Acetaminophen is detailed in the table below.[9]

Table 3. Acetaminophen Drug Information

SCIENTIFIC NAME ACETAMINOPHEN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Q81
Drug Class	OTHER ANALGESICS AND ANTIPYRETICS
Drug Sub-class	ANILIDES
ATC Code	N02BE01
Pharmacological Class (ASHP)	Non opioid analgesics
DRUG INFORMATION	
Dosage Form	Tablets (for adults) Syrup (for pediatrics)
Route of Administration	Oral administration
Dose (Adult) [DDD]*	1g every 6hours
Maximum Daily Dose Adults*	4g
Dose (pediatrics)	10 to 15 mg/kg/dose every 4 to 6 hours
Maximum Daily Dose Pediatrics*	75mg/kg
Adjustment	Use with caution in patients with hepatic diseases. Limited, low-dose therapy is usually well-tolerated.
Prescribing edits*	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A

MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Acute hepatotoxicity may result from intentional or unintentional overdose in adult and pediatric patients.
Drug Interactions	**Category X:** • Metyrapone
Special Population	N/A
Pregnancy	Acetaminophen crosses the placenta. The use of acetaminophen in recommended doses during pregnancy has not been associated with an increased risk of miscarriage or still birth; however, an increase in fetal death or spontaneous abortion may be seen following maternal overdose if treatment is delayed.
Lactation	Acetaminophen is present in breast milk. Nonopioid analgesics are preferred for lactating patients who require pain control.
Contraindications	N/A
Monitoring Requirements	Serum acetaminophen levels.
Precautions	In patients with G6PD deficiency or hepatic impairment. When used for self-medication, patients should be aware if symptoms get worse or new symptoms appear.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for acetaminophen in pain management for patients with EB. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Acetaminophen

Acetaminophen, also known as Paracetamol, is a widely used analgesic and antipyretic medication. Its mechanism of action involves inhibition of the enzyme cyclooxygenase, primarily in the central nervous system, which results in reduced synthesis of prostaglandins. In the context of EB, acetaminophen is often employed to manage pain associated with blistering and wound care, providing symptomatic relief for individuals with this condition. The usual dose depends on factors such as age and weight, with careful consideration given to avoid exceeding recommended limits to prevent potential liver toxicity. For adults, the recommended dose is 1g every 6 hours, with a maximum daily dose of 4g. In pediatrics, the dosage is 10 to 15 mg/kg/dose, administered every 4 to 6 hours, with a maximum daily dose of 75mg/kg/day. Common side effects are generally mild but may include nausea and allergic reactions. Importantly, paracetamol is generally considered safe for use in pregnant and breastfeeding women when used at recommended doses. Its use during pregnancy is often preferred over other pain medications. Due to its favorable safety profile when used within recommended doses, paracetamol is a preferred option for pain management in EB, providing essential relief without exacerbating the skin fragility characteristic of the condition. As always, individuals with EB should consult with healthcare professionals for personalized guidance on medication use. There are no recommendations issued by the HTA bodies for Acetaminophen.

2.1.2 Ibuprofen

Information on Ibuprofen is detailed in the table below.[10]

Table 4. Ibuprofen Drug Information

SCIENTIFIC NAME IBUPROFEN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes

PMDA	Yes
Indication (ICD-10)	Q81
Drug Class	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
Drug Sub-class	PROPIONIC ACID DERIVATIVES
ATC Code	M01AE01
Pharmacological Class (ASHP)	Non opioid analgesics, Nonsteroidal anti-inflammatory drugs.
DRUG INFORMATION	
Dosage Form	Tablets (for adults) Oral suspensions (for pediatrics)
Route of Administration	Oral administration
Dose (Adult) [DDD]*	200 to 400 mg every 4 to 6 hours as needed or 600 to 800 mg every 6 to 8 hours as needed.
Maximum Daily Dose Adults*	3.2g
Dose (pediatrics)	4 to 10 mg/kg/dose (maximum dose: 600 mg/dose) every 6 to 8 hours.
Maximum Daily Dose Pediatrics*	40mg/kg
Adjustment	If CrCl ≤ 30 mL/minute, avoid use due to increased risk of acute kidney injury.
Prescribing edits*	**AGE**
AGE (Age Edit):	Ibuprofen is not recommended for children weighing less than 7 kg or 6 months.
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Cardiovascular effects: acute myocardial infraction, cerebrovascular accident and hypertension.

	• Gastrointestinal effects: gastrointestinal ulcer and inflammation • Hematological effects: prolonged bleeding time. • Hepatic effects: transaminase elevation. • Kidney effects: Hemodynamically mediated acute kidney injury, interstitial nephritis (with or without nephrotic syndrome), and renal papillary necrosis.
Drug Interactions	**<u>Category X:</u>** • Abrocitinib • Acemetacin • Ketorolac • Aminolevulinic Acid • Macimorelin • Mifamurtide
Special Population	N/A
Pregnancy	The use of nonsteroidal anti-inflammatory drugs close to conception may be associated with an increased risk of miscarriage due to cyclooxygenase-2 inhibition interfering with implantation. Treatment in pregnant women should be individualized.
Lactation	Ibuprofen is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother
Contraindications	Hypersensitivity to ibuprofen (anaphylactic reactions, serious skin reactions) or any component of the formulation, history of asthma, urticaria, or allergic-type reaction to aspirin.
Monitoring Requirements	Monitor response (pain, range of motion, grip strength, mobility, ADL

	function), inflammation; observe for weight gain, edema; monitor renal function
Precautions	May cause CNS effects (dizziness, drowsiness), hyperkalemia, ophthalmic events (blurred vision). May increase the risk of aseptic meningitis and bronchospasm in sensitive patients.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for ibuprofen in pain management for patients with EB. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Ibuprofen

Ibuprofen, a nonsteroidal anti-inflammatory drug, exerts its analgesic, anti-inflammatory effects by inhibiting the enzyme cyclooxygenase (COX), which plays a role in the synthesis of prostaglandins. In the management of EB, ibuprofen is used to alleviate pain and reduce inflammation associated with blistering. The usual dose varies based on factors such as age, weight, and the severity of symptoms. However, caution is advised in individuals with EB due to the potential risk of gastrointestinal irritation and increased bleeding tendencies. For adults, the recommended dose is 200 to 400 mg every 4 to 6 hours as needed, or 600 to 800 mg every 6 to 8 hours as needed, with a maximum daily dose of 3.2g. In pediatrics, the dosage is 4 to 10 mg/kg/dose, with a maximum single dose of 600 mg, administered every 6 to 8 hours, and a maximum daily dose of 40mg/kg/day. Common side effects include gastrointestinal discomfort, and in rare cases, more serious complications like ulcers or bleeding may occur. Ibuprofen is generally not recommended during the third trimester of pregnancy, and caution is advised during breastfeeding, with consultation with healthcare professionals recommended for personalized guidance. There are no recommendations issued by the HTA bodies for Ibuprofen.

2.2 Topical Antibiotics

2.2.1 Fusidic Acid

Information on Fusidic acid is detailed in the table below.[11]

Table 5. Fusidic Acid Drug Information

SCIENTIFIC NAME FUSIDIC ACID	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Q81
Drug Class	ANTIBIOTICS FOR TOPICAL USE
Drug Sub-class	OTHER ANTIBIOTICS FOR TOPICAL USE
ATC Code	D06AX01
Pharmacological Class (ASHP)	Topical antibiotics
DRUG INFORMATION	
Dosage Form	Ointment and gel.
Route of Administration	Topical usage.
Dose (Adult) [DDD]*	Apply small amount to affected area 2 to 3 times daily for 7 to 14 days. If a gauze dressing is used, frequency of application may be reduced to once or twice daily.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Apply small amount to affected area 2 to 3 times daily for 7 to 14 days. If a gauze dressing is used, frequency of application may be reduced to once or twice daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing edits*	**QL**
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	Fusidic acid should be used for up to 14 days.
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Application site irritation, pruritis.
Drug Interactions	N/A
Special Population	N/A
Pregnancy	Fusidic acid crosses the placenta following systemic administration. Systemic absorption following topical application is minimal.
Lactation	It is not known if fusidic acid is present in breast milk following topical application.
Contraindications	Hypersensitivity to fusidic acid or any component of the formulation.
Monitoring Requirements	N/a
Precautions	Superinfections in prolonged use and skin reactions
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for fusidic acid the management of wounds infections in patients with EB. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Fusidic acid

Topical fusidic acid exerts its antimicrobial effects by inhibiting bacterial protein synthesis, specifically targeting the ribosomal translocation step. In the context

of EB, fusidic acid is commonly employed for the topical treatment of wound infections caused by susceptible bacteria. The recommended dose may vary depending on the severity and extent of the infection, and it is typically applied to the affected area two to three times daily. Fusidic acid plays a crucial role in preventing and treating bacterial infections in the fragile skin of individuals with EB, contributing to the overall wound care management and minimizing the risk of complications associated with bacterial colonization. There are no recommendations issued by the HTA bodies for Fusidic acid.

2.3 Opioids Analgesics

2.3.1 Morphine Sulfate

Information on Morphine sulfate is detailed in the table below.[12]

Table 6. Morphine Sulfate Drug Information

SCIENTIFIC NAME MORPHINE SULFATE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Q81
Drug Class	OPIOIDS
Drug Sub-class	NATURAL OPIUM ALKALOIDS
ATC Code	N02AA01
Pharmacological Class (ASHP)	Opioid analgesics
DRUG INFORMATION	
Dosage Form	Prolonged released tablets Solution for injection
Route of Administration	Oral administration Intravenous administration
Dose (Adult) [DDD]*	Oral: 5 to 15 mg every 4 hours as needed. IV: 1 to 4mg every 1 to 4h as needed.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Infants ≤6 months:**

	• Oral (0.08 to 0.1 mg/kg every 3 to 4 hours). • IV (0.025 to 0.05 mg/kg every 2 to 4 hours). • Continuous IV Infusion (0.008 to 0.02 mg/kg/hour). **Infants > 6 months, Children (Weight < 50 kg):** • Oral (0.15 to 0.3 mg/kg every 3 to 4 hours). • IV (0.05 to 0.1 mg/kg every 2 to 4 hours). • Continuous IV Infusion (0.01 to 0.04 mg/kg/hour). **Children and Adolescents (Weight ≥ 50 kg):** • Oral (10 to 20 mg every 3 to 4 hours). • IV (2 to 5 mg every 2 to 4 hours). • Continuous IV Infusion (1.5 mg/hour).
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal impairment:** • CrCl ≥60 mL/minute: No dosage adjustment necessary. • CrCl 30 to <60 mL/minute: Consider use of an alternative opioid analgesic. If necessary, administer 50% to 75% of usual initial dose; may also consider extending dose interval. Titrate cautiously to response. • CrCl 15 to <30 mL/minute: Avoid use. If necessary, administer 25% to 50% of usual initial dose; may also consider extending dose interval. Titrate cautiously to response. • CrCl <15 mL/minute: Avoid use.
Prescribing edits*	**PA, QL, ST**
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	Prior authorization is required for opioid therapy, in order to review pain severity, the risk of substance abuse, starting dose, maximum dose and duration.
QL (Quantity Limit):	Reassess use in 3-7 days.
ST (Step Therapy):	Strong opioids are used for neuropathic pain after failure of other treatment options like tramadol or gabapentin.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Opioid induced constipation • Opioid induced respiratory depression • Opioid induced withdrawal • Pruritus
Drug Interactions	**Category X:** • Azelastine • Bromperidol • Flunarizine • Kratom • Monoamine oxidase inhibitors • Naltrexone • Paraldehyde • Thalidomide • Olopatadine • Orphenadrine • Oxomemazine
Special Population	Use with caution in old patients.
Pregnancy	Morphine crosses the placenta. While morphine and other opioids can be used judiciously for pain management during pregnancy, careful monitoring, shared decision-making, and consideration of alternative pain management strategies are crucial to

	minimize potential risks to both the mother and the infant. Healthcare providers should follow established guidelines and engage in informed discussions with patients to ensure safe and effective pain management during this critical period.
Lactation	Morphine is present in breast milk. Careful consideration and monitoring are essential when using morphine in breastfeeding women. Prioritizing nonopioid analgesics, employing the lowest effective opioid doses, and actively monitoring both mother and infant can contribute to safe and effective pain management while breastfeeding. Healthcare providers should follow established guidelines and maintain open communication with patients to ensure the well-being of both mother and infant during this critical period.
Contraindications	Hypersensitivity to morphine or to any component of the formulation, symptoms of respiratory depression, GI problems, use of monoamine oxidases inhibitors.
Monitoring Requirements	• Symptoms of respiratory depression • Symptoms of hypersensitivity • Pain control • Signs of substance abuse
Precautions	Disease related concerns: • CNS depression • Hyperalgesia • Hypotension • Constipation • Obesity • Renal impairment • Withdrawal

Black Box Warning	Addiction, abuse, and misuse; life threatening respiratory depression; neonatal opioid withdrawal syndrome; and risks from concomitant use with benzodiazepines or other CNS depressants.
REMS*	Adherence to REMS requirements is essential for healthcare providers prescribing opioid analgesics. Completion of REMS-compliant education, comprehensive counseling of patients and caregivers, and promotion of safe use practices contribute to the overarching goal of ensuring the safe and responsible use of opioid analgesics, minimizing the risks associated with these medications.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of neuropathic pain treatment options in EB patients by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for morphine sulfate.**

Table 7. Morphine Sulfate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Morphine sulfate	NICE[13]	**February 2016** The comparative effectiveness and cost-effectiveness of morphine versus ketamine as first-line pharmacological pain management for patients with major trauma, in both pre-hospital and hospital settings, are under scrutiny. While opioids, particularly morphine, have been conventionally used for analgesia in such cases, their association with negative side effects prompts an examination of intravenous ketamine in sub-anesthetic doses as an alternative.

		Intriguingly, some studies suggest that combining intravenous morphine with ketamine may offer more effective analgesia than morphine alone. However, there is a paucity of evidence from well-controlled trials directly comparing the effectiveness and side effects of morphine and ketamine, highlighting the importance of investigating this aspect in the context of pain management after major trauma. If intravenous access has not been established, consider the intranasal route for atomized delivery of diamorphine or ketamine.
	CADTH	N/A
	HAS[14]	Favorable opinion for the continued inclusion of morphine sulfate in the list of reimbursable medications for social security beneficiaries in the following indications: - Severe and/or refractory pain not responding to lower-level analgesics, severe cancer-related pain, severe acute non-cancerous pain (post-operative pain), and severe chronic neuropathic pain. - Intense and/or refractory pain associated with knee or hip osteoarthritis and chronic low back pain. The Commission reiterates its unfavorable opinion for the continued inclusion on the list of reimbursable medications for social security beneficiaries in the indication: - Intense or refractory pain in all other situations of non-cancerous and non-neuropathic chronic pain, particularly in chronic inflammatory rheumatic diseases, primarily represented by rheumatoid arthritis and spondylarthritis.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Morphine sulfate

Morphine sulfate, an opioid analgesic, primarily acts on the central nervous system by binding to specific receptors, mainly mu-opioid receptors. This binding results in the modulation of pain perception and transmission, leading to pain relief. In the context of EB, morphine sulfate may be prescribed to manage severe neuropathic pain associated with the condition, offering relief to patients experiencing chronic discomfort. The dosage of morphine sulfate for EB can vary depending on the severity of pain and individual patient factors. The typical oral dose is 5 to 15 mg every 4 hours as needed, while the IV dose ranges from 1 to 4 mg every 1 to 4 hours as needed. However, caution is warranted in pregnant and breastfeeding women, as morphine can cross the placenta and transfer to breast milk. While the use of morphine during pregnancy may pose risks, healthcare providers may consider its limited and judicious use when the benefits outweigh potential risks. In breastfeeding women, close monitoring for potential side effects, such as sedation or respiratory depression in the infant, is crucial, and healthcare providers may recommend alternative pain management strategies, when possible, to minimize exposure. Common side effects of morphine sulfate include nausea, constipation, drowsiness, and respiratory depression. As with any medication, decisions regarding the use of morphine sulfate in pregnant or breastfeeding individuals should be made based on a thorough assessment of the risks and benefits by healthcare professionals. HAS has issued positive recommendations regarding the use of morphine sulfate in managing neuropathic pain associated with EB patients.

2.3.2 Tramadol

Information on Tramadol is detailed in the table below.[15]

Table 8. Tramadol Drug Information

SCIENTIFIC NAME TRAMADOL	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	Q81
Drug Class	Analgesic
Drug Sub-class	Opioid

ATC Code	N02A
Pharmacological Class (ASHP)	Opioid agonist analgesics
DRUG INFORMATION	
Dosage Form	Film-coated tablet or capsule
Route of Administration	Oral use
Dose (Adult) [DDD]	**Acute pain (eg, postoperative):** **Immediate release: Oral: Initial:** 50 mg every 4 to 6 hours as needed; if rapid onset of analgesic effect is required, may consider an initial dose of 50 to 100 mg every 4 to 6 hours; some experts suggest that 25 to 50 mg 3 times per day may be sufficient for patients with moderate acute pain. Increase dose as needed and tolerated to 50 to 100 mg every 4 to 6 hours. **Chronic pain (alternative agent):** **Immediate release: Oral:** The ideal dosing regimen has not been established; consider restricting the initial dose to <300 mg tramadol per day (ie, <50 mg *morphine equivalents daily*). An example initial dose is 25 to 50 mg every 6 hours as needed. The dose may be increased as needed and tolerated to 50 to 100 mg every 4 to 6 hours (maximum: 400 mg/day). **Extended release: Initial: Oral:** 100 mg once daily; titrate by 100 mg/day increments every 5 days as needed.
Maximum Daily Dose Adults	Maximum daily dose: 400 mg/day.
Dose (pediatrics)	**Acute pain: Immediate-release formulations:** **Children and Adolescents ≤16 years:** **Limited data available: Oral:** 1 to 2 mg/kg/dose every 4 to 6 hours; maximum single dose: 100 mg (usual adult starting dose: 50 to 100 mg); maximum daily dose is the lesser of 8 mg/kg/day or 400mg/day. Note: Due to

	potential respiratory complications, tramadol should be avoided in patients <12 years of age and all pediatric patients undergoing tonsillectomy and/or adenoidectomy. **Adolescents ≥17 years: Oral:** 50 to 100 mg every 4 to 6 hours; maximum daily dose: 400 mg/day. For patients not requiring rapid onset of effect, tolerability to adverse effects may be improved by initiating therapy at 25 mg/day and titrating dose by 25 mg every 3 days until 25 mg 4 times daily is reached. Dose may then be increased by 50 mg every 3 days as tolerated to reach 50 mg 4 times daily. **Chronic pain: Extended-release formulations: Adolescents ≥18 years: Oral:** -Patients not currently on immediate-release tramadol: 100 mg once daily; titrate every 5 days; maximum daily dose: 300 mg/day. -Patients currently on immediate-release tramadol: Calculate 24-hour total immediate-release tramadol dose and initiate total extended-release daily dose (round dose to the next lowest 100 mg increment) once daily; titrate as tolerated to desired effect; maximum daily dose: 300 mg/day.
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Altered kidney function**: CrCl ≥30 mL/minute: Immediate release, extended release: No dosage adjustment necessary. CrCl <30 mL/minute: Immediate release: Increase dosing interval to every 12 hours; maximum: 200 mg/day. ER formulation should be avoided.
Prescribing edits	**AGE**

AGE (Age Edit):	Tramadol use should be avoided in all pediatric patients < 12 years.
CU (Concurrent Use Edit):	N/A
G (Gender Edit): N/A	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**>10%:** -**Gastrointestinal:** Constipation, dyspepsia, nausea, xerostomia -**Nervous system:** Dizziness, drowsiness, headache, vertigo **1% to 10%:** -**Cardiovascular:** Chest pain, flushing, hypertension, orthostatic hypotension, peripheral edema, vasodilation -**Dermatologic:** Dermatitis, diaphoresis, pruritus, skin rash -**Endocrine & metabolic:** Hot flash, hyperglycemia, menopausal symptoms, weight loss -**Gastrointestinal:** Abdominal pain, anorexia, decreased appetite, diarrhea, flatulence, vomiting -**Genitourinary:** Pelvic pain, prostatic disease, urinary frequency, urinary retention, urinary tract infection -**Nervous system:** Agitation, anxiety, apathy, asthenia, ataxia, chills, confusion, depersonalization, depression, euphoria, falling, hypertonia.
Drug Interactions	**Category X:** Bromperidol Dapoxetine

	Carbamazepine Dapoxetine Fexinidazole Flunarizine Fusidic Acid (Systemic)
Special Population	**Elderly >65 years to ≤75 years:** Refer to adult dosing; use with caution and initiate at the low end of the dosing range. **Elderly >75 years:** Immediate release: Maximum: 300 mg/day. Extended release: Use with extreme caution.
Pregnancy	Tramadol, a commonly used opioid, can traverse the placenta, exposing the fetus to its effects. Maternal opioid use, including tramadol, has been linked to adverse outcomes such as poor fetal growth, stillbirth, and preterm delivery. Prolonged in utero exposure to opioids, including tramadol, may lead to Neonatal Abstinence Syndrome. Symptoms include irritability, sleep disturbances, tremors, increased muscle tone, and gastrointestinal dysfunction. Abrupt discontinuation is discouraged, and tapering should be considered, balancing the risks to both the pregnant patient and the fetus.
Lactation	Tramadol, along with its potent M1 metabolite, is detected in breast milk, with M1 exhibiting stronger opioid activity than tramadol itself. The extent of exposure to a breastfeeding infant is influenced by the mother's CYP2D6 metabolism. The manufacturer advises against the use of tramadol during breastfeeding due to the potential for severe adverse effects in the infant, including excessive sedation and

	respiratory depression. For lactating patients requiring pain control around childbirth or for postpartum surgeries, nonopioid analgesics are preferred. In cases where opioids are necessary, the recommendation is to use the lowest effective dose for the shortest possible duration to minimize risks for both the mother and the breastfeeding infant.
Contraindications	-Hypersensitivity (eg, anaphylaxis) to tramadol, opioids, or any component of the formulation -Pediatric patients <12 years of age -Postoperative management in pediatric patients <18 years of age who have undergone tonsillectomy and/or adenoidectomy -Significant respiratory depression -Acute or severe bronchial asthma in the absence of appropriately monitored settings and/or resuscitative equipment -GI obstruction -Concomitant use with or within 14 days following monoamine oxidase inhibitor therapy.
Monitoring Requirements	Pain relief; respiratory and mental status/alertness (especially in patients on concomitant CNS depressants, including benzodiazepines); blood pressure; heart rate; blood glucose if hypoglycemia is suspected; signs/symptoms of hyponatremia (eg, confusion, disorientation) especially during initiation of therapy; bowel function; signs/symptoms of tolerance, substance use disorder, abuse, misuse, or suicidal ideation; signs or symptoms of hypogonadism or hypoadrenalism; signs and symptoms of serotonin syndrome such as mental status changes (eg, agitation, hallucinations,

	coma), autonomic instability (eg, tachycardia, labile BP, hyperthermia), neuromuscular changes (eg, hyperreflexia, incoordination), and/or GI symptoms (eg, nausea, vomiting, diarrhea); signs and symptoms of neonatal withdrawal syndrome in infants born to mothers using opioids during pregnancy (eg. irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight); during discontinuation of therapy monitor pain control, withdrawal symptoms, mood changes, suicidal ideation, and for use of other substances.
Precautions	***Concerns related to adverse effects:*** · Hypotension ***Disease-related concerns:*** • **Abdominal conditions:** May obscure diagnosis or clinical course of patients with acute abdominal conditions. • **Adrenocortical insufficiency:** Long-term opioid use may cause secondary hypogonadism, which may lead to mood disorders and osteoporosis. • **Biliary tract impairment:** Use caution in patients with biliary tract dysfunction or acute pancreatitis; opioids may cause spasm of the sphincter of Oddi. • **CNS depression/coma:** Avoid use in patients with impaired consciousness or coma as these patients are susceptible to intracranial effects of CO_2 retention. • **Diabetes** • **Delirium tremens** • **Head trauma** • **Hepatic impairment:** ER formulations should not be used in severe hepatic impairment (Child-Pugh class C).

	• **Mental health conditions:** Use opioids with caution for chronic pain in patients with mental health conditions (eg, depression, anxiety disorders, posttraumatic stress disorder) due to potential increased risk for opioid use disorder and overdose. • **Obesity** • **Renal impairment** • **Sleep-related disorders** • **Suicide risk** • **Thyroid dysfunction** ***Special populations:*** • **CYP2D6 "poor metabolizers":** Poor metabolizers have decreased metabolism of tramadol to its active metabolite, which may diminish analgesia; avoid the use of tramadol and consider alternatives that are not metabolized by CYP2D6. • **CYP2D6 "ultrarapid metabolizers":** Ultrarapid metabolizers have increased metabolism of tramadol to its active metabolite, which may increase the risk of toxicity; avoid the use of tramadol and consider alternatives that are not metabolized by CYP2D6. •**Pediatric: Respiratory depression:** Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
Black Box Warning	-Risk of medication errors -Addiction, abuse, and misuse -Opioid analgesic Risk Evaluation and Mitigation Strategy (REMS)

	-Life-threatening respiratory depression: -Accidental ingestion -Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children -Neonatal opioid withdrawal syndrome: -Interactions with drugs affecting cytochrome P450 isoenzymes -Risks from concomitant use with benzodiazepines or other CNS depressants
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of EB treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Tramadol.**

Table 9. Tramadol HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tramadol	NICE[16]	**September 2020** Management recommendations for neuropathic pain (excluding trigeminal neuralgia) encompass the option to initiate treatment with amitriptyline, duloxetine, gabapentin, or pregabalin. Tramadol may be considered for acute rescue therapy, but caution is advised for its long-term use.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Tramadol

Tramadol is recommended for the management of neuropathic pain, excluding trigeminal neuralgia. Furthermore, tramadol may be considered for acute rescue therapy and caution is advised regarding its prolonged use. As a commonly used opioid, tramadol can cross the placenta, exposing the fetus to potential adverse effects, such as poor fetal growth, stillbirth, and preterm delivery. Prolonged utero exposure may result in Neonatal Abstinence Syndrome, characterized by symptoms like irritability, sleep disturbances, tremors, increased muscle tone, and gastrointestinal dysfunction. Abrupt discontinuation is discouraged, and tapering should be considered, carefully weighing the risks for both the pregnant patient and the fetus. Importantly, tramadol use is not recommended in pediatric patients under 12 years of age.

2.4 Anti-Epileptic Agents

2.4.1 Gabapentin

Information on Gabapentin is detailed in the table below.[12]

Table 10. Gabapentin Drug Information

SCIENTIFIC NAME GABAPENTIN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Q81
Drug Class	ANTIEPILEPTICS
Drug Sub-class	OTHER ANTIEPILEPTICS
ATC Code	N03AX12
Pharmacological Class (ASHP)	Anticonvulsants
DRUG INFORMATION	
Dosage Form	Capsules or tablets
Route of Administration	Oral administration
Dose (Adult) [DDD]*	100 to 300mg, 1 to 3 times daily. increase dose based on response and tolerability to a target dose range of 300 mg to 1.2 g 3 times daily.

<table>
<tr><td></td><td>If extended release, the dose is 300mg once daily.</td></tr>
<tr><td>Maximum Daily Dose Adults*</td><td>3.6g</td></tr>
<tr><td>Dose (pediatrics)</td><td>5 mg/kg/dose 1 to 3 times daily</td></tr>
<tr><td>Maximum Daily Dose Pediatrics*</td><td>3600mg</td></tr>
<tr><td>Adjustment</td><td>
<table>
<tr><th>CrCl (mL/minute)[c]</th><th>Approximate Maintenance Dose Adjustment</th><th>Maximum Maintenance Dose</th></tr>
<tr><td>>79</td><td>No dose adjustment necessary</td><td>3,600 mg/day in 3 divided doses</td></tr>
<tr><td>50 to 79</td><td>No dose adjustment necessary, not to exceed 1,800 mg/day</td><td>1,800 mg/day in 3 divided doses</td></tr>
<tr><td>30 to 49</td><td>~50% reduction</td><td>900 mg/day in 2 to 3 divided doses</td></tr>
<tr><td>15 to 29</td><td>~75% reduction</td><td>600 mg/day in 1 to 2 divided doses</td></tr>
<tr><td><15</td><td>~90% reduction</td><td>300 mg/day in 1 dose</td></tr>
</table>
Hemodialysis, intermittent (thrice weekly): 100 3 times per week after hemodialysis.
Peritoneal dialysis: 100mg every other day.

<u>Hepatic impairment:</u>
Consider dosage adjustment in patients with preexisting liver cirrhosis (child-Turcotte-Pugh class B and C:
Oral: Initial: ≤300 mg per day in 1 to 3 divided doses; may titrate as tolerated to the usual indication-specific maximum recommended dose).</td></tr>
<tr><td>Prescribing edits*</td><td>N/A</td></tr>
<tr><td>AGE (Age Edit):</td><td>N/A</td></tr>
<tr><td>CU (Concurrent Use Edit):</td><td>N/A</td></tr>
<tr><td>G (Gender Edit):</td><td>N/A</td></tr>
<tr><td>MD (Physician Specialty Edit):</td><td>N/A</td></tr>
<tr><td>PA (Prior Authorization):</td><td>N/A</td></tr>
<tr><td>QL (Quantity Limit):</td><td>N/A</td></tr>
<tr><td>ST (Step Therapy):</td><td>N/A</td></tr>
<tr><td>EU (Emergency Use Only):</td><td>N/A</td></tr>
<tr><td>PE (Protocol Edit):</td><td>N/A</td></tr>
<tr><td colspan="2">SAFETY</td></tr>
<tr><td>Main Adverse Drug Reactions (Most common and most serious)</td><td>• CNS and respiratory depression
• Hypersensitivity reactions (immediate or delayed)</td></tr>
</table>

	• Neuropsychiatric effects (emotional lability) • Suicidal ideation
Drug Interactions	**<u>Category X:</u>** • Azelastine • Bromperidol • Flunarizine • Kratom • Olopatadine • Orphenadrine • Oxomemazine
Special Population	N/A
Pregnancy	Gabapentin crosses the placenta. Data collection to monitor pregnancy and infant outcomes following exposure to gabapentin are still ongoing.
Lactation	Gabapentin is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Based on limited data, gabapentin is considered relatively compatible with breastfeeding; infants should be monitored for drowsiness, adequate weight gain, and developmental milestones
Contraindications	Hypersensitivity to gabapentin or to any component of the formulation.
Monitoring Requirements	• Periodic renal function • Suicidality • Symptoms of respiratory depression • Symptoms of hypersensitivity
Precautions	Disease related concerns: • Myasthenia gravis • Renal impairment • Seizure disorder Other precautions:

	Withdrawal: antiseizure medications should not be discontinued abruptly because of the possibility of increasing seizure frequency in patients with epilepsy or other withdrawal symptoms.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of neuropathic pain treatment options in EB patients by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Gabapentin.**

Table 11. Gabapentin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Gabapentin	NICE[17]	NICE recommends the use of gabapentin as an initial treatment for neuropathic pain (except trigeminal neuralgia). If the initial treatment is not effective or not tolerated, other drugs can be considered. However, it is important to note that gabapentin is a Class C controlled substance and should be evaluated carefully for a history of drug abuse before prescribing. Patients should also be observed for signs of abuse and dependence.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Gabapentin

Gabapentin, functioning as an anticonvulsant and analgesic, modulates its mechanism of action by binding to the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. In the realm of pain management for EB, gabapentin is occasionally prescribed to mitigate neuropathic pain associated with the condition. The typical dose is contingent upon individual patient factors, commencing with a low dose (100 to 300mg, 1 to 3 times daily) and gradually titrating upward (300 mg to 1.2 g, 3 times daily). Common adverse reactions may encompass dizziness, drowsiness, and peripheral edema. Noteworthy is the careful consideration and consultation required for gabapentin's utilization in pregnant and breastfeeding women. Although data on its safety during pregnancy is limited, an assessment of potential risks and benefits is crucial, necessitating decisions made in consultation with a healthcare provider. NICE has issued positive recommendations regarding the use of gabapentin in managing neuropathic pain associated with EB patients.

2.5 NMDA Receptor Antagonists

2.5.1 Ketamine

Information on Ketamine is detailed in the table below.[18]

Table 12. Ketamine Drug Information

SCIENTIFIC NAME KETAMINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	Q81
Drug Class	Dissociative anesthetic
Drug Sub-class	NMDA receptor antagonists
ATC Code	N01AX03
Pharmacological Class (ASHP)	NMDA receptor antagonists
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	IV, SubQ, Intranasal

Dose (Adult) [DDD]	**Analgesia, subanesthetic dosing (off-label use):** **Acute pain:** **IV: Initial:** 0.25 to 0.5 mg/kg bolus (maximum bolus: 35 mg), followed by 0.05 to 0.25 mg/kg/hour continuous infusion in patients who need a longer duration of analgesia; titrate to pain goal and tolerability; usual dosing range: 0.05 to 1 mg/kg/hour; may need to use doses at the higher range in patients who are opioid-tolerant or with opioid-induced hyperalgesia; duration of infusion: 48 to 72 hours. **Intranasal (off-label route):** 0.2 to 1 mg/kg by administering half dose in each nostril (using 100 mg/mL solution); if necessary, may repeat after 10 to 15 minutes with 0.25 to 0.5 mg/kg; titrate to pain goal and tolerability. Doses up to 40 mg may be reliably administered intranasally; for doses >40 mg, part of the dose will be delivered to the oropharynx and ingested orally due to volume limitations, which may decrease effectiveness. **Chronic pain, intractable:** **IV intermittent infusion: Initial:** 0.25 to 0.6 mg/kg (usual maximum dose: 60 mg) as a 4- to 6-hour infusion; titrate to pain goal and tolerability; repeat daily for up to 2 to 10 days as needed. **IV continuous infusion: Initial:** 0.05 to 0.15 mg/kg/hour for 1 day outpatient or for 2 to 5 days inpatient; titrate to pain goal and tolerability; usual dosing range: 0.02 to 1 mg/kg/hour (maximum dose: 30 mg/hour; not well established). **SubQ:** Initial: 0.1 to 0.6 mg/kg (usual 2.5 to 25 mg) as needed; titrate to pain goal and tolerability. In patients who need a

	longer duration of analgesia, follow with continuous SubQ infusion at 0.1 to 1.2 mg/kg/hour (maximum daily dose: 500 mg). **Oral: Note: Used in refractory chronic pain (eg, advanced illness or palliative care) in a hospitalized patient when other regimens have failed.** Initial: 0.5 mg/kg/day administered in 3 to 4 divided doses as needed; then increase dose in increments of ~5 mg/dose based on pain goal and tolerability; maximum daily escalation dose: 15 to 20 mg; maximum dose: 800 mg/day. **Note: May administer dose as the undiluted injectable or mixed with an appropriate flavoring agent (eg, simple syrup).**
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**Analgesia, acute pain (low dose; sub-dissociative):** Very limited data available: Optimal dose not established. **Children ≥3 years and Adolescents: Intranasal:** Usual: 1 mg/kg/dose, may repeat once; range: 0.5 to 1.5 mg/kg/dose; maximum dose: 100 mg/dose.
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	**AGE**
AGE (Age Edit):	The American College of Emergency Physicians considers the use of ketamine in infants <3 months of age to be an absolute contraindication, due to the higher risk of airway complications.
CU (Concurrent Use Edit):	N/A
G (Gender Edit): N/A	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A

QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**>10%:** Nervous system: Prolonged emergence from anesthesia (12%; includes agitation, confusion, delirium, dreamlike state, excitement, hallucinations, irrational behavior, vivid imagery).
Drug Interactions	**Category X:** Azelastine (Nasal) Bromperidol Flunarizine Orphenadrine Oxomemazine
Special Population	**Pediatric neurotoxicity:** In pediatric and neonatal patients <3 years of age and patients in third trimester of pregnancy, the repeated or lengthy exposure to sedatives or anesthetics during surgery/procedures may have detrimental effects on child or fetal brain development and may contribute to various cognitive and behavioral problems.
Pregnancy	Ketamine, known to traverse the placenta, exhibits dose-dependent increases in uterine contractions during pregnancy, with effects that may vary across trimesters. The drug's plasma clearance is diminished in pregnancy, and the administration of large doses at delivery has been associated with dose-related neonatal depression and decreased Apgar scores. Despite the manufacturer's non-recommendation for obstetric use, ketamine has been explored for cesarean and vaginal

	deliveries, and it may be considered as an alternative induction agent in hemodynamically unstable females requiring general anesthesia for cesarean delivery.
Lactation	The presence of ketamine in breast milk remains uncertain. The Academy of Breastfeeding Medicine suggests delaying elective surgery until breastfeeding is well-established, with the recommendation to express milk before the procedure when feasible. Generally, for healthy, full-term infants, breastfeeding can resume, or expressed milk can be given once the mother is awake and in recovery. In cases where infants are at risk for apnea, hypotension, or hypotonia, storing milk for later use during lower-risk periods is advised. While small supplemental doses of ketamine during cesarean delivery are deemed acceptable and should not hinder breastfeeding once the mother is stable and alert, insufficient data exists to support its use for long-term pain control according to the Academy of Breastfeeding Medicine.
Contraindications	-Hypersensitivity to ketamine or any component of the formulation -Conditions in which an increase in blood pressure would be hazardous -History of cerebrovascular accident -Severe cardiac decompensation
Monitoring Requirements	-Heart rate, blood pressure, respiratory rate, transcutaneous O_2 saturation, level of sedation, emergence reactions -Cardiac function (continuously monitored in patients with increased blood pressure or cardiac decompensation)

	-LFTs, alkaline phosphatase, and gamma glutamyl transferase (baseline and then at periodic intervals).
Precautions	***Concerns related to adverse effects:*** • CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery, driving). • Increased intracranial pressure: Some consider the use of ketamine in patients with CNS masses, CNS abnormalities, or hydrocephalus a relative contraindication due to multiple reports that ketamine may increase intracranial pressure in these patients; use caution, especially at higher doses. • Increased ocular pressure • Liver injury: Recurrent use (eg, abuse/misuse, medically supervised unapproved use) may cause hepatobiliary dysfunction (usually a cholestatic pattern) and biliary duct dilatation with or without evidence of biliary obstruction. • Porphyria: The ACEP considers the use of ketamine in patients with porphyria a relative contraindication due to enhanced sympathomimetic effect produced by ketamine. ***Disease-related concerns:*** • Cerebrospinal fluid pressure elevation: Use with caution in patients with cerebrospinal fluid pressure elevation • Ethanol use: Use with caution in patients with chronic alcohol use disorder or who are acutely alcohol intoxicated
Black Box Warning	N/A

REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of EB options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Ketamine.**

Table 13. Ketamine Drug Information

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ketamine	NICE[13]	**February 2016** The comparative effectiveness and cost-effectiveness of morphine versus ketamine as first-line pharmacological pain management for patients with major trauma, in both pre-hospital and hospital settings, are under scrutiny. While opioids, particularly morphine, have been conventionally used for analgesia in such cases, their association with negative side effects prompts an examination of intravenous ketamine in sub-anesthetic doses as an alternative. Intriguingly, some studies suggest that combining intravenous morphine with ketamine may offer more effective analgesia than morphine alone. However, there is a paucity of evidence from well-controlled trials directly comparing the effectiveness and side effects of morphine and ketamine, highlighting the importance of investigating this aspect in the context of pain management after major trauma. If intravenous access has not been established, consider the intranasal route for atomized delivery of diamorphine or ketamine.
	CADTH[19]	**May 2020** Ketamine is a medication that has been explored for its use in pain management, particularly for chronic non-cancer pain. Studies have shown that

		IV ketamine infusions can significantly reduce pain scores and increase positive response rates in the short term. However, the long-term pain control effects of ketamine are limited and may vary among patients. It is important to note that the evidence for the use of ketamine in chronic pain management is limited, and there are no explicit recommendations regarding its use in current guidelines. Additionally, the studies reviewed did not assess the impact of ketamine on quality of life or compare its effectiveness to other pharmacological treatments.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- ketamine

Ketamine, explored for its potential in pain management, has demonstrated short-term efficacy in reducing pain scores and increasing positive response rates, particularly through IV infusions for chronic non-cancer pain. However, evidence supporting its long-term effectiveness is limited and varies among patients. Current guidelines lack explicit recommendations for ketamine use in chronic pain management, with studies not assessing its impact on quality of life or comparing it to other treatments. The comparative effectiveness and cost-effectiveness of morphine versus ketamine for major trauma patients are under investigation, considering the negative side effects associated with opioids. Some studies suggest that combining intravenous morphine with ketamine may enhance analgesia. In pregnancy, ketamine, though known to traverse the placenta, has been explored for obstetric use, including cesarean deliveries, despite dose-related neonatal depression concerns and the manufacturer's non-recommendation for such use.

2.6 Other Drugs

Drugs detailed below are not registered by the SFDA.

2.6.1 Oleogel S10

Oleogel-S10, which contains 10% birch triterpenes formulated with sunflower oil, received approval from the European Medicines Agency in June 2022 for treating partial-thickness wounds associated with dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB) in patients aged six months and older. Subsequently, in September 2022, the United Kingdom Medicines and Healthcare products Regulatory Agency also granted approval for Oleogel-S10.

Functioning as a sterile topical gel, Oleogel-S10 plays a role in various stages of the wound-healing process. This includes the modulation of inflammatory mediators, stimulation of keratinocyte migration, and promotion of differentiation.

2.6.2 Beremagene Geperpavec (B-VEC)

In May 2023, the US Food and Drug Administration granted approval for beremagene geperpavec (B-VEC) to treat wounds in patients aged six months and older afflicted with dystrophic epidermolysis bullosa (DEB) resulting from variants in the COL7A1 gene. B-VEC, a modified herpes simplex virus 1 vector, lacks replication ability and integration. It is applied topically to deliver a functional version of the COL7A1 gene directly to skin cells, aiming to restore the production of type VII collagen in DEB patients.

Administration: B-VEC is applied to selected wounds in evenly spaced droplets once weekly.

Table 14. Beremagene Geperpavec Dose by Wound Size

Wound area	Dose	Volume
< 20 cm^2	4 × 10^8 plaque-forming units	0.2 mL
20 to < 40 cm^2	8 × 10^8 plaque-forming units	0.4 mL
40 to 60 cm^2	1.2 × 10^9 plaque-forming units	0.6 mL

2.6.3 Tricyclic Antidepressants

2.6.3.1 Amitriptyline

Information on Amitriptyline is detailed in the table below.[19]

Table 15. Amitriptyline Drug Information

SCIENTIFIC NAME AMITRIPTYLINE	
US FDA	N/A
EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	Q81
Drug Class	Antidepressant
Drug Sub-class	Tricyclic Antidepressant
ATC Code	N06AA09
Pharmacological Class (ASHP)	Tricyclic Antidepressant
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	**Neuropathic pain, chronic (off-label use): Oral:** Initial: 10 to 25 mg once daily at bedtime; may gradually increase dose based on response and tolerability in 10 to 25 mg increments at intervals ≥1 week up to a usual dosage range of 25 to 125 mg/day once daily at bedtime or in 2 divided doses.
Maximum Daily Dose Adults	Maximum: 150 mg/day given once daily at bedtime or in 2 divided doses
Dose (pediatrics)	**Chronic pain management:** Limited data available: Children and Adolescents: Oral: Initial: 0.1 mg/kg at bedtime; may advance as tolerated over 2 to 3 weeks to 0.5 to 2 mg/kg at bedtime.
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments provided in manufacturer's labeling; however, hepatically metabolized, use with caution.
Prescribing edits	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A

G (Gender Edit): N/A	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Cardiovascular:** Acute myocardial infarction, atrioventricular conduction disturbance, cardiac arrhythmia, cardiomyopathy, cerebrovascular accident, ECG changes, edema, exacerbation of cardiac disease, facial edema, heart block, hypertension, orthostatic hypotension, palpitations, sinus tachycardia, syncope **Dermatologic:** Allergic skin rash, alopecia, diaphoresis, skin photosensitivity, urticarial **Endocrine & metabolic:** Altered serum glucose, decreased libido, galactorrhea not associated with childbirth, gynecomastia, increased libido, SIADH, weight gain, weight loss **Gastrointestinal:** Ageusia, anorexia, constipation, melanoglossia, nausea, paralytic ileus, parotid gland enlargement, stomatitis, unpleasant taste, vomiting, xerostomia **Genitourinary:** Breast hypertrophy, impotence, testicular swelling, urinary frequency, urinary retention, urinary tract dilation **Hematologic & oncologic:** Eosinophilia, purpuric disease **Hepatic:** Hepatic failure, hepatitis (rare; including altered liver function and jaundice) **Hypersensitivity:** Tongue edema

	Neuromuscular & skeletal: Asthenia, lupus-like syndrome, tremor **Ophthalmic:** Accommodation disturbance, blurred vision, increased intraocular pressure, mydriasis
Drug Interactions	**<u>Category X:</u>** Bromopride Bromperidol Cimetropium: Cisapride Dapoxetine Dronedarone Glycopyrrolate (Oral Inhalation) Flunarizine Ipratropium (Oral Inhalation) Linezolide Monoamine Oxidase Inhibitors (Antidepressant) Sélégiline
Special Population	N/A
Pregnancy	Amitriptyline, a tricyclic antidepressant, crosses the human placenta, and while case reports suggest potential CNS effects, limb deformities, and developmental delay, a definitive causal relationship has not been established. Tricyclic antidepressants, including amitriptyline, may be linked to irritability, jitteriness, and rare convulsions in neonates. Neonates exposed during pregnancy might experience increased crying, constipation, urination problems, respiratory distress, and nausea.
Lactation	Amitriptyline and its metabolite, nortriptyline, are present in breast milk, as evidenced by data from various sources. Studies suggest that the estimated exposure of breastfeeding infants to amitriptyline ranges from

	0.2% to 1.9% of the weight-adjusted maternal dose, with a relative infant dose reported to be approximately 1% to 3%. The World Health Organization considers amitriptyline compatible with breastfeeding at doses up to 150 mg/day.
Contraindications	Hypersensitivity to amitriptyline or any component of the formulation; coadministration with or within 14 days of MAOIs; coadministration with cisapride; acute recovery phase following myocardial infarction.
Monitoring Requirements	Serum sodium in at-risk populations (as clinically indicated); mental status and alertness; closely monitor all patients for depression, clinical worsening, suicidality, psychosis, or unusual changes in behavior (such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, and social functioning), particularly during the initial 1 to 2 months of therapy or during periods of dosage adjustments (increased or decreases); heart rate, BP, and ECG in older adults and patients with pre-existing cardiac disease; electrolyte panel (to assess risk of conduction abnormalities); blood glucose; weight and BMI; blood levels are useful for therapeutic monitoring; Monitor for signs/symptoms of serotonin syndrome such as mental status changes (eg, agitation, hallucinations, delirium, coma).
Precautions	***Disease-related concerns:*** • **Cardiovascular disease:** Use with caution in patients with a history of cardiovascular disease (including

	previous MI, stroke, tachycardia, or conduction abnormalities). • **GI motility:** Use with caution in patients with decreased GI motility (eg, paralytic ileus) as anticholinergic effects may exacerbate underlying condition. • **Hepatic impairment:** Use with caution in patients with hepatic impairment; clearance is decreased, and plasma concentrations are increased. Due to the narrow therapeutic index, use lower initial and maintenance doses of tricyclic antidepressants. Use caution in patients with hepatic encephalopathy due to the risk of neurocognitive effects**.** • **Mania/hypomania:** May precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Combination therapy with an antidepressant and a mood stabilizer should also be avoided in acute mania or mixed episodes, as well as maintenance treatment in bipolar disorder due to the mood-destabilizing effects of antidepressants. • **Myasthenia gravis:** Use with caution in patients with myasthenia gravis; may exacerbate condition. • **Ophthalmic conditions:** Use with caution in patients with certain ophthalmic conditions (eg, increased intraocular pressure, narrow angle glaucoma, visual problems) as anticholinergic effects may exacerbate underlying condition. • **Renal impairment:** Use with caution in patients with renal impairment. • **Seizure disorder:** Use with caution in patients at risk of seizures, including those with a history of seizures, head

	trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. • **Urinary retention** (eg, benign prostatic hyperplasia): Use with caution in patients with urinary retention as anticholinergic effects may exacerbate underlying condition.
Black Box Warning	The use of antidepressants, including amitriptyline, has been associated with an elevated risk of suicidal thoughts and behaviors (suicidality) in children, adolescents, and young adults during short-term studies. Individuals contemplating the use of amitriptyline. It's essential to note that amitriptyline is not approved for use in pediatric patients.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of EB options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Amitriptyline.**

Table 16. Amitriptyline HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Amitriptyline	NICE[16]	**September 2020** Management recommendations for neuropathic pain (excluding trigeminal neuralgia) encompass the option to initiate treatment with amitriptyline, duloxetine, gabapentin, or pregabalin. Offer amitriptyline as an initial treatment option for neuropathic pain (except trigeminal neuralgia). If amitriptyline is not effective or not tolerated, other drugs can be considered.

	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Amitriptyline

Amitriptyline is recommended for the management of neuropathic pain, excluding trigeminal neuralgia, as an initial treatment, but if it proves ineffective or is not well-tolerated, alternative medications can be considered. The usual dosage range is 25 to 125 mg/day once daily at bedtime or in 2 divided doses. Amitriptyline crosses the placenta, with case reports suggesting potential CNS effects, limb deformities, and developmental delay in exposed infants. Caution is advised due to the association of antidepressants, including amitriptyline, with an elevated risk of suicidal thoughts and behaviors in children, adolescents, and young adults during short-term studies.

Section 3.0 Key Recommendations

EB is a diverse set of inherited mechanobullous disorders characterized by variable skin and mucosa fragility resulting from mutations affecting structural proteins in the skin. The condition encompasses four primary types EBS, JEB, DEB, and KEB. The severity of EB varies among its subtypes, determined by blistering intensity and the specific mutation. Currently, there is no targeted therapy for EB, although research in this area is actively ongoing. The predominant approach to treatment is supportive, encompassing wound care, infection control, nutritional assistance, and the prevention and management of complications. It involves a multidisciplinary team, typically consisting of a dermatologist, an EB nurse specializing in wound care, a primary care provider, an occupational therapist, a nutritionist, and a social worker. Additional consultation with specialists such as those in gastroenterology, ophthalmology, nephrology, hematology, endocrinology, cardiology, pain management, psychiatry, genetics, plastic surgery, and specialized dentistry is pursued as necessary.

Skin And Wound Care: (B)

- Bathing can be a painful experience, especially for those with severe forms and open wounds. Clinical observations suggest that using saltwater resembling isotonic saline significantly reduces pain during bathing. For neonates, warmed bags of normal saline can be utilized in small baby bathtubs.
- Regarding wound dressing, nonstick or nonadherent silicone dressings and absorbent foam dressings are recommended as primary dressings for EB wounds. These can be covered with absorbent padding and left in place for several days, with no added benefit from expensive nonstick dressings used as a secondary layer. Bath soaking facilitates painless removal of adherent dressings.
- Wounds with bacterial colonization or infection may necessitate more frequent changes and specific dressing types. Fusidic acid is recommended for the topical treatment of wound infections in patients with EB. The suggested frequency is two to three times daily, and there are no specific HTA recommendations for this topical treatment.
- Novel topical wound therapies: A noteworthy breakthrough is the FDA's approval in May of Krystal Biotech’s beremagene geperpavec (B-VEC; Vyjuvek), a non-invasive topical gene therapy for the treatment of DEB. Oleogel-S10 (Filsuvez), approved in Europe for EB, has shown efficacy in JEB and DEB patients.
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Oral And Dental Lesions

- Individuals with EB often experience prominent oral bullae, ulcers, and erosions, with limited research exploring therapeutic interventions for these manifestations.
- Strategies for managing oral lesions in EB include the use of mouthwashes and oral gels specifically designed to address mucositis. Products such as Gelclair®, K-trix® (calendula-based), and Dentoxol® are commonly prescribed. Some individuals also employ gargling with saltwater as a cost-effective alternative, although scientific evidence supporting its effectiveness in EB is currently lacking.
- Effective oral hygiene is crucial for individuals with EB, and chlorhexidine 0.12% is frequently recommended to prevent oral diseases. This antiseptic has demonstrated effectiveness against candida, though it has proven ineffective in controlling caries. Various application methods, such as mouthwashes, swabs, sprays, gels, and topical varnish applications, have been employed. In patients with oral lesions, alcohol-free formulations are advised to avoid additional irritation.
- For dental care in children with EB, caregivers are encouraged to initiate tooth brushing as soon as the child's teeth emerge. Fluoridated toothpaste is recommended, with appropriate dosages based on the child's age. Topical applications of high-dose fluoride varnish are recommended every 3 months, especially for those at high risk of caries. Fluoride can be administered in various forms, including foam, gel preparation, or mouthwash, and gel preparations can be applied using a toothbrush, a custom-made plastic tray, or with the use of cotton rolls. Regular preventive treatment protocols may involve rinsing twice a day for two weeks every three months.

Pain And Itch Management

- Pain is a persistent aspect of EB and a significant aspect of its management. The origin of pain in EB can be intrinsic, stemming from factors like skin blisters, wounds, oral or corneal erosions, and dental issues, or it can be triggered by activities such as bathing or dressing changes.
- Mild to moderate pain can be addressed with analgesics, such as acetaminophen, either alone or in combination with Ibuprofen. Tramadol is suggested for moderate pain, while morphine is reserved for severe pain.
- Gabapentin can serve as adjuvant therapy for severe chronic pain associated with blistering. Furthermore, chronic pruritus, a debilitating feature of EB, can be addressed with measures such as antihistamines and oral gabapentin. C

- Amitriptyline is recommended for the management of neuropathic pain, excluding trigeminal neuralgia, as an initial treatment, but if it proves ineffective or is not well-tolerated, alternative medications can be considered.
- Ketamine, explored for its potential in pain management, has demonstrated short-term efficacy in reducing pain scores and increasing positive response rates, particularly through IV infusions for chronic non-cancer pain. Current guidelines lack explicit recommendations for ketamine use in chronic pain management.

Nutritional Support

- All patients with severe forms of EB, particularly RDEB or JEB, experience nutritional compromise and require nutritional support.
- Nutritional support aims to alleviate stress associated with feeding difficulties, address macro- and micronutrient deficiencies, promote normal bowel function, optimal growth rates, immune status, wound healing, and overall mobility and quality of life.
- Regular monitoring of micronutrient levels, including iron, calcium, vitamin D, zinc, selenium, and vitamins, is essential, and supplementation should be tailored to address deficiencies.

Physical and psychological therapies

- For chronic pain management use CBT. B
- For acute pain management, offer the patient distraction, hypnosis, visualization, relaxation, or other forms of CBT. B
- Consider habit reversal training, and other psychological techniques for management of pruritus. C

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of epidermolysis bullosa.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group.

Appendix C. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
((((epidermolysis bullosa[MeSH Terms]) OR (Epidermolysis Bullosa Acquisita[Title/Abstract])) OR (Epidermolysis Bullosa Dystrophica[Title/Abstract])) OR (Epidermolysis Bullosa Simplex[Title/Abstract])) OR (Epidermolysis Bullosa, Junctional[Title/Abstract])	In the last 5 years	("epidermolysis bullosa"[MeSH Terms] OR "epidermolysis bullosa acquisita"[Title/Abstract] OR "epidermolysis bullosa dystrophica"[Title/Abstract] OR "epidermolysis bullosa simplex"[Title/Abstract] OR "epidermolysis bullosa junctional"[Title/Abstract]) AND (y_5[Filter])	951

Appendix D. Treatment Algorithm for Epidermolysis Bullosa

Wound care	• Topical antibiotics (fusidic acid). • Specialized dressings. • Cleaning solutions (saline or chlorhexidine) and debridement.
Oral care	• Oral hygiene and antiseptics. • Dental referral, education and preventive measures.
Pain management	• Mild pain (acetaminophen and/or ibuprofen). • Moderate pain (tramadol). • Severe pain (morphine, ketamine). • Chronic pain (gabapentin, amitriptylline).
Nutritional support	• Well balanced diet • Supplements in potential deficiencies
Physical and psychological therapies	• Motion exercises for maintaining joint mobility.