Topical Opioids: The "Solution" to the Opioid Epidemic

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Levi M. Hall, PharmD, BCPS

Disclosures

- Nothing to disclose

Learning Objectives

- Summarize current literature supporting topical opioid administration for pain
- Describe the pharmacokinetic and pharmacodynamic properties of topical morphine
- Identify medical staff and patient/family education needs and implementation strategy
- Explore logistics of adding topical morphine to a health system formulary, establishing medication prescribing guidelines, developing of an order set in electronic health record, and identifying a list of approved prescribers

PAINWEEK

Outline

- General Topical Medications
- What Exists Now: Topical Opioids
- EBM Publications
- Patient Cases
- Logistics: Formulary, Guidelines/Policies, Compounding, Dispensing
- Safety and Monitoring

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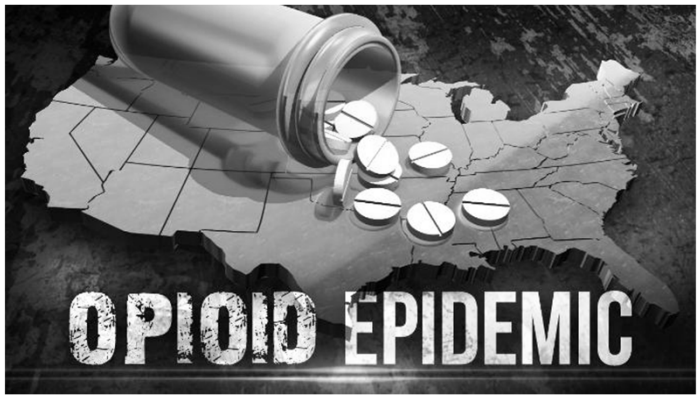
Opioid commission tells Trump to declare state of emergency



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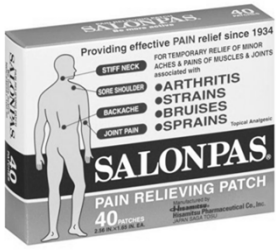
Examples of Commercially Available OTC Topical Analgesics



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Common Rx Topical Pain Agents

- Amantadine (5-20%)
- Amitriptyline (2-10%)
- Baclofen 2%
- Bupivacaine (2-5%)
- Carbamazepine 5%
- Clonidine (0.1-0.3%)
- Cyclobenzaprine (1-3%)
- Dextromethorphan (5-10%)
- Diclofenac (1-10%)
- Gabapentin (5-10%)
- Guaifenesin (10-40%)
- Ibuprofen (10-40%)
- Indomethacin (10-40%)
- Ketamine (5-10%)
- Ketoprofen (10-50%)
- Lidocaine (2-10%)
- Loperamide 1%
- Nifedipine (2-16%)
- Orphenadrine (5-10%)
- Phenytoin (2-10%)
- Piroxicam (0.5-2%)
- Tetracaine (0.5-10%)
- Topiramate 1%

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Ladd,E,PharmD,TopicalPain medications Another Approach to Pain. 2013;8

Transdermal Treatment

- Transdermal delivery allows drugs to solubilize in order to penetrate the tissue layers
- Gels form liposomes that carry the drug down between the cells of the dermis and epidermis
- Minimizes side effects by delivering drug to the site of injury
- Research confirms peripheral site of action for many of these drugs

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Ladd,E,PharmD,TopicalPainmedications.Another Approach to Pain.2013;8

Current Data

- Several small case series have shown rapid relief using topical opioids in patients with pain due to skin infiltration of tumor, skin ulcers of malignant and nonmalignant origin, several oral mucositis, and knee arthritis
- Monitoring and drug interactions of topical opioids is same as systemic opioids (excess sedation, respiratory depression, pruritus)

Gallagher RE, Arndt DR, Hunt K. Analgesic effects of topical methadone; a report of four cases. Clin J Pain. 2005;21:190-192.

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Theoretical Mechanisms of Action

- Topically applied opioids have provided effective analgesia without adverse effects in adult patients with painful inflammatory conditions
- The presumed mechanism of action is by interaction with opioid receptors that are sited on sensory nerve terminals, and which may be upregulated in inflammation
- A solution may provide rapid reduction in pain scores in patients without reported adverse effects or tolerance

Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. J Pain Symptom Manage. 2005; 29:118-119.

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Theoretical Mechanisms of Action (cont'd)

- The insight that opioids exert a local analgesic effect is based on several observations:
  - Opioid receptors have been found on peripheral nerves and inflamed tissue
  - Morphine and its metabolites are largely undetectable systemically when applied topically to skin ulcers (suggesting the analgesic effect is local)
  - Peripheral opioid injections for local analgesia, such as intra-articular morphine after knee surgery, have been found to be effective in several trials

Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. J Pain Symptom Manage. 2005; 29:118-119.

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Medication Delivery Methods

- Mouthwash
  - Tetracaine HCl
  - Corticosteroids
  - Antifungal
  - Antiviral
  - Antibiotics
  - Antihistamine
  - Sucralfate
  - Antifoaming mouthwash base
- Mouth gel
  - Slow release protective coating
- Mouthwash
  - Medications to coat the mouth, treat pain, infections
- Mouth gel
  - Morphine sulfate
  - Hydromorphone HCl
  - Glycerin
  - Lemon
  - Bioadhesive slow released gel

Recent advances in novel drug delivery system. Vol. 1 No. 9 2012
www.thepharmajournal.com

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Medication Delivery: Wound Gels

- Wound dressing gel
  - Aqueous gel, glycol base gel
  - Polyox bandage
- Wound dressing gels
  - Lidocaine
  - Tetracaine
  - Morphine sulfate
  - Hydromorphone HCl
  - Methadone HCl

Recent advances in novel drug delivery system. Vol. 1 No. 9 2012
www.thepharmajournal.com

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Medication Delivery: Wound Gels (cont'd)

- For bed sore ulcer wounds
  - Same pain medications
  - Aloe vera
  - Phenytoin
  - Misoprostol
- Metronidazole base
- Bases
  - Intrasite gel
  - Solosite
  - Cellulose (med visc) gel
  - Propylene glycol
  - Ethoxy diglycol
  - DMAE

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Medication Delivery: Topical Spray

- Topical spray
  - 0.1 mL per spray
  - 2 to 4 sprays to surrounding area or specific painful spots
- Topical sprays
  - Morphine sulfate
  - Hydromorphone HCl
  - Methadone HCl
  - Normal saline
  - Propylene glycol
  - Ethoxy diglycol
  - DMAE

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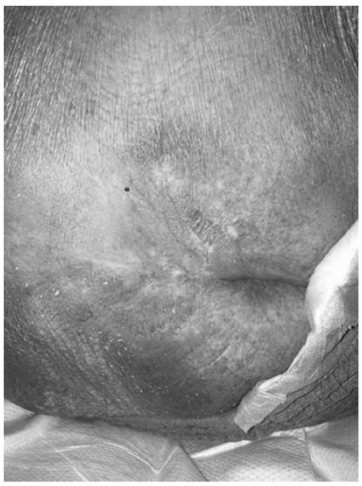
Medication Delivery: Radiation Burn

- Radiation burn gel
  - Lidocaine
  - Tetracaine
  - Morphine
  - Hydromorphone
  - NSAID
  - Antibiotics
  - Aloe vera
  - Pluronic F127 gel (carbomer gel)



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PAIN® 154 (2013) 1920–1928

PAIN®

www.elsevier.com/locate/pain

Topical review

How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review

Tanya Graham [a,*], Patricia Grocott [a], Sebastian Probst [b], Steven Wanklyn [c], Jacqueline Dawson [c], Georgina Gethin [d]

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[b] Zurich University of Applied Sciences, Zurich, Switzerland
[c] Guys and St Thomas's NHS Foundation Trust, London, UK
[d] National University of Ireland, Galway, Ireland

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Topical Opioids Literature Review

- Literature review of topical opioids for painful cutaneous lesions
- 27 articles included, 170 patients total
- Variations in size and etiology of wounds, prep and application of topical opioids, dosage, frequency of application
- Aspects requiring monitoring: local adverse effects, systemic absorption, drug interactions

Graham T, Grocott P, Probst S, et al. How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. Pain. 2013; 154 (10): 1920–1928

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Topical Opioids Literature Review (cont'd)

- Results of review indicated that topical opioids are clinically useful and safe for controlling inflammatory pain in wounds
- Systemic absorption occurs at a safe level
- Large amount of variability amongst the available data
- Systematic approaches are required to establish effectiveness and dose-response relationship of clinical opioids to inform clinical guidelines

Graham T, Grocott P, Probst S, et al. How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. Pain. 2013; 154 (10): 1920–1928

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EBM Review of Wound Treatment

CURRENT OPINION

Evidence-based approach to manage persistent wound-related pain

Kevin Y. Woo[a,b], Laura K. Abbott[a], and Lawrence Librach[c,d]

Purpose of review
Pain is a significant concern in people with chronic wounds. A systematized approach is recommended for the management of wound-associated pain with the objectives to address pain relief, increase function, and restore overall quality of life.

Recent findings
Combinations of pharmacological agents are often recommended based on varying degree of pain severity, coexisting nociceptive and neuropathic pain, and chronic inflammation related to wound-associated pain. Topical agents including morphine, tricyclic antidepressants (e.g., amitriptyline), nonsteroidal anti-inflammatory drugs (NSAIDs), capsaicin, ketamine, and lidocaine/prilocaine provide pain relief with minimal side effects. Mindful dressing selection to minimize trauma, handle excess fluid, and prevent periwound skin damage has been shown to reduce persistent wound pain. To avoid nocebo hyperalgesia, it is important to address emotions, anticipation or negative expectation of discomfort.

Summary
Pain is a complex biopsychosocial phenomenon that requires multiple pharmacological and nonpharmacological management approach.

Keywords
nocebo, pain management, persistent wound-related pain

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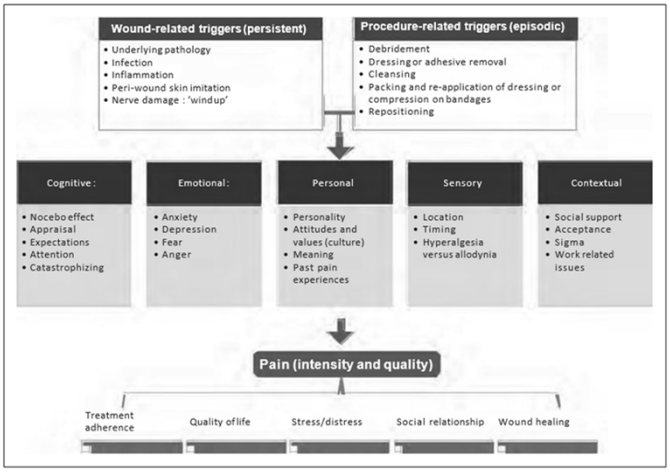
Curr Opin Support Palliat Care 2013;7:86-94.

Total Pain Assessment



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Curr Opin Support Palliat Care 2013;7:86-94.

Checklist

Table 4. UPPER and LOWER wound infection checklist

Clinical evaluation of wound infection	Definition
UPPER	Signs and symptoms related to critical colonization due to infection damage in the upper wound compartment
U – unhealthy tissue	Presence of > 50% of debris, red friable tissue or abnormal discoloration of granulation tissue
P – pain	Sudden emergence of increase in pain
P – poor healing	Changes in wound size of less than 10% in last 7 days
E – exudate	Moderate to heavy amount of exudate
R – reek	Presence of foul odor
LOWER	Signs and symptoms of wound infection related to bacterial damage in the lower or deeper wound compartment
L – Larger in size	Increase in wound size or new areas of satellite breakdown
O – osseous tissue	Wound that probes to bone
W – warmth	Increased periwound temperature of more than 2.8F compared with temperature in proximal area
E – edema	Mild-to-moderate edema
R – redness	Redness of >2 cm beyond wound margin

Curr Opin Support Palliat Care 2013;7:86-94.

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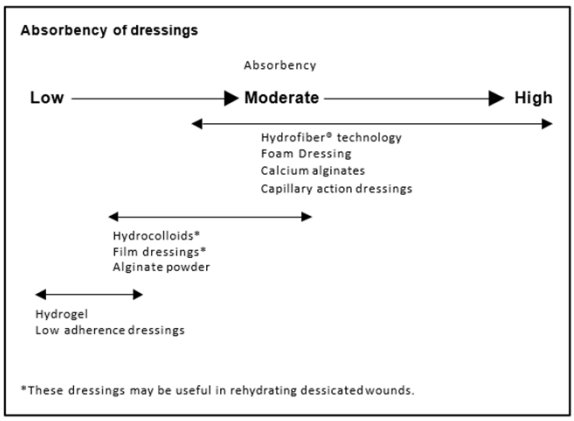
Compound Base Considerations



Curr Opin Support Palliat Care 2013;7:86-94.

Wound Assessment

Wound management in advanced illness

Table 3. Strategies to protect periwound skin

Types	Description	Application
Silicone	Silicones are polymers that include silicon together with carbon, hydrogen and oxygen	Apply to periwound skin
Zinc oxide	An inorganic compound that is insoluble in water	Apply generous to skin. No need to remove all residual prior to each application
Acrylates	Film-forming skin preparation to form a protective interface on skin attachment sites	Spray or wipe on skin sparingly
Hydrocolloid	A hydrocolloid wafer consists of a backing with carboxymethylcellulose as the filler, water absorptive components, such as gelatin and pectin (commercial gelatin desserts) and an adhesive.	Window frame the stoma to prevent recurrent stripping of skin

Curr Opin Support Palliat Care 2013;7:86-94.

Northamptonshire Healthcare NHS

GUIDELINES FOR THE USE OF TOPICAL MORPHINE FOR PAINFUL SKIN ULCERS IN PALLIATIVE CARE

Policy Details	
NHFT document reference	MMG029
Version	Version 1 – November 2012
Date Ratified	07.12.12
Ratified by	Medicines Management Committee
Implementation Date	07.12.12
Responsible Director	Medical Director
Review Date	07.12.14
Related Policies & other documents	MMP001 – Control of Medicines Policy
Freedom of Information category	Guideline

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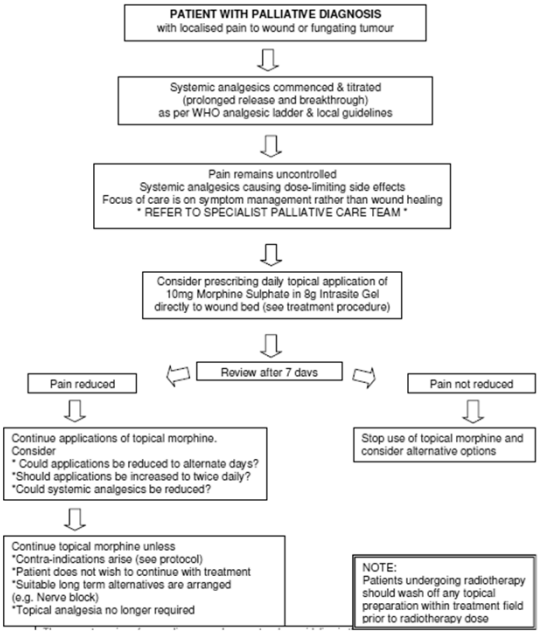
NHA Foundation 2012: Use of topical morphine



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NHA Foundation 2012: Use of topical morphine

Effect on Wound Healing

- Still remains controversial in published literature
- More recent publications are questioning the theory that opioids impair wound healing
  - 'Improved healing after 4 weeks of morphine gel application'
  - 'Area under the gel healed more quickly than usual'
- Postulated to have anti-inflammatory effect within the wound, and morphine may act as an endothelial growth promoting and angiogenic growth factor

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Watterson G, Howard R, Goldman A. Arch Dis Child 2004;89:679–81.
Twillman RK *et al*. *J Pain Symptom Manage* 1999; 17: 288–292.

Final Compound We Use

- Morphine 10 mg (1 mL)
- Solosite 10 gm 0.1% w/w (9 mL)
- **Total: 10 mL**

- Morphine 10 mg (1 mL)
- Solosite 10 gm 0.1% w/w (9 mL)
- Lidocaine 2% 300 mg (15 mL)
- **Total: 25 mL**

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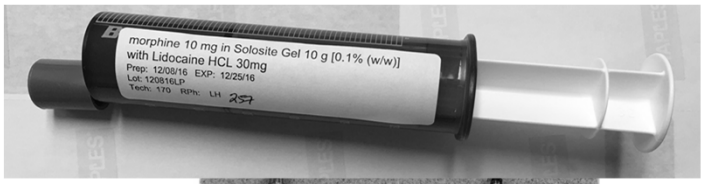
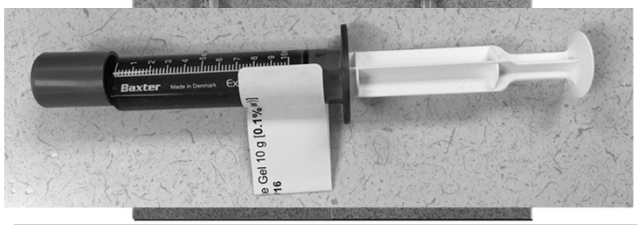
Morphine w/w/o Lidocaine Solution





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Compound Recording Example

Beaumont
Department of Pharmaceutical Services

BATCH COMPOUNDING RECORD – NON-STERILE PREPARATIONS

Morphine 10 mg in 10 g Solosite gel (0.1% w/w):

BATCH/LOT NUMBER:

REFERENCES:
*

Example Label
Click above to PRINT labels

INGREDIENTS *(Name, Strength, Concentration, Volume)*	MANUFACTURER & NDC NUMBER	MANUFACTURER LOT NUMBER & EXPIRATION	Assembled By: (Tech)	RPh Pre-CHECK	Amount to use per container	Batch Factor	Amount used in This Batch	Prepared By: (Tech)	RPh Post-CHECK
Morphine 10 mg/mL carpuject					1 mL	x	=		
Solosite gel					10 mL	x	=		
						x	=		

COMPOUNDING INSTRUCTIONS:

1. Obtain 2 – 60 mL leur lock syringes and a 3 way stopcock adaptor.
2. Clean the area for compounding with isopropyl alcohol and don gloves, bonnet, and mask.
3. Remove the syringes from packaging and pull the plunger out of one of the syringes.
4. Eject Solosite contents into open syringe. Replace plunger and use sterilized clip to remove additional air from syringe and measure to needed volume. Attach adaptor.
5. Using other syringe, draw up morphine contents into syringe. Connect to other leur end of adaptor.
6. Push contents from morphine syringe through adaptor into gel syringe. Push back into other syringe again. Perform this mixing 10 times in each direction. At end, all contents should be in 1 syringe. Remove empty syringe.
7. Using empty 10 mL oral syringes and oral syringe/leur-lock adaptor, inject 10 mL into each syringe.
8. Seal syringe with tamper evident cap. Label. Add "for topical use only" sticker.
9. Store in 6CN Pyxis for dispensing.

TOTAL QUANTITY COMPOUNDED:
(Strength/Conc/Volume)

COMPOUNDING EQUIPMENT USED:
(if applicable)

PACKAGING & *STORAGE:

- ☐ Room Temp Expires in 28 days
- ☐ Refrigerated Expires in_____days
- ☐ Frozen Expires in_____days

****BUD Date:_____***

Must include information source(s) (i.e. USP 795, published manuscript, etc) for storage and BUD beyond use dating in "REFERENCES" section above.
**Must include specific storage location of component(s) in all instances that a specific product/concentration is required for batch preparation.*
***Beyond use date (BUD): the date after which a compound preparation shall not be used.*

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Key Questions to Consider

Ask questions like these listed below.
Is your staff properly trained and evaluated in nonaseptic manipulation skills, gowning technique, and compounding room use?
Do you have systems in place for handling complaints and investigating adverse events?
Do you purchase pharmaceutical-grade chemicals (USP, NF equivalent) from FDA-registered suppliers?
Do you obtain Certificate of Analyses for all formula ingredients?
Do you maintain both master formulas and lot-specific worksheets for all compounds?
Can you immediately trace a prescription back to original formula log sheet and source of ingredients?
Is every step of the compounding process from prescribing to compounding and labeling through dispensing reviewed and verified by a licensed pharmacist?
Do you verify potency of finished compounds via weight, volume, and yield checks; can you share results within 48 hours?
Are your pharmacists, technical and customer care staff dedicated to compounding?

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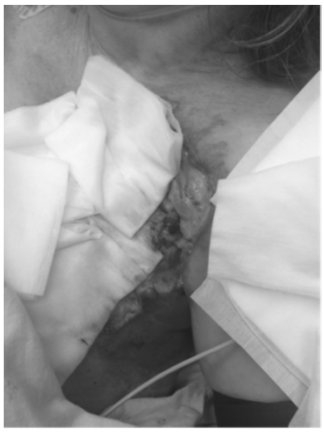
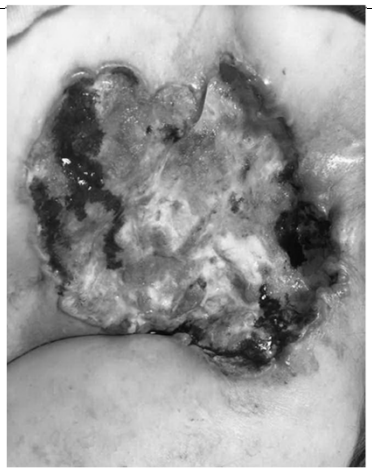
Ladd E.,TopicalPainmedications: Another Approach to Pain.2013;8.

Patient Case





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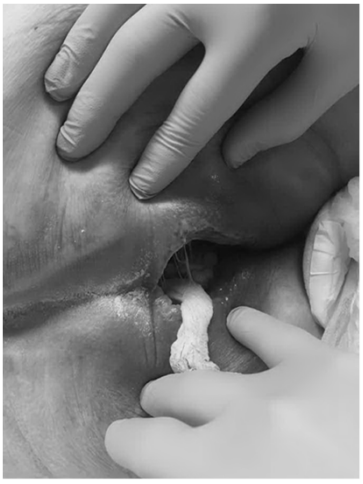
Patient Case (cont'd)

- Colorectal excision with rectal reconstruction, rectal cancer
- Prior to topical morphine, patient required 500 mg oral morphine equivalent
- With topical morphine gel, reduced to 20 mg of oxycodone per day



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Indications for Use

- Due to difficulty with medication procurement (resources needed for extemporaneous compounding), patients must be reviewed by a specialist
- The following criteria should be followed:
  - Terminal or palliative care patients only
  - Painful superficial chronic wounds (broken skin) <10 cm diameter
  - Non-neuropathic, localized pain
  - Opioid naïve patients, history of addiction to drug or alcohol—only where the introduction of systemic opioids would be inappropriate, or is refused by the individual patient
  - Opioid tolerant patients—only where the side effects prevent adequate dose escalation of the systemic opioid dose

NHA Foundation 2012: Use of topical morphine

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Exclusion Criteria

- Hypersensitivity (eg, rash) to morphine or other opioid derivatives
- Children and individuals ≤18 years of age
  - Do not use in or around the eyes because the products are not suitable for such applications
  - Do not use in wounds with excessive exudate or bleeding because the gel will not adhere to the wound surface
    - Topical morphine causes vasodilation leading to more bleeding
  - Acute respiratory depression
  - Topical management of infected wounds—systemic treatment should be considered

NHA Foundation 2012: Use of topical morphine

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Administration

- Apply entire contents of syringe **topically** to each wound with each dressing change, up to a maximum of 3 times per day
- Nurse must use gloved hand to evenly distribute medication throughout entire wound
- Nurse to dispose of glove and topical syringe in the sharps container (in compliance with controlled substance disposal policy)
- Do NOT apply external heat to wound
- Apply ordered dressings to wound following medication application
- Patient to avoid showering, bathing, or washing application sites for at least 1 hour

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Adverse Effects

- Monitoring is the same as systemic opioids
  - Excess sedation
  - Respiratory depression
  - Pruritus
- Drug interactions: CNS depressants, opioid agonists, sedatives, and hypnotics (additive respiratory and CNS depressive effects)

NHA Foundation 2012: Use of topical morphine

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Cautions

- Intolerance to systemic side effects of morphine or other opioid derivatives
- Severe renal impairment (eGFR <30ml/min) or severe hepatic impairment
  - Used in preference to systemic treatments for this very reason
- Severe impairment of central nervous system (head injury or raised intracranial pressure)
  - Used in preference to systemic opioids to reduce the risks of side effects
- Monitor carefully for signs of opioid accumulation and toxicity over time
- Care in bleeding or exuding wounds due to reduced inability of the Intrasite® gel or chosen base to adhere to wound surface
  - Morphine has vasodilatory effect and may increase bleeding if hemostatis not achieved
- Hydrogels have a propensity to macerate if left on too long or if an excessive amount of the gel is applied

NHA Foundation 2012: Use of topical morphine

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Adverse Effects

- Very few side effects have been reported within the literature available regarding the use of transdermal morphine
- There is a potential for systemic absorption especially over large areas or with higher concentrations
- Patients should be monitored closely for opioid side effects, especially if taking systemic opioids concomitantly
- Pruritus, burning, and discomfort at site of application of morphine gel has been reported when using Intrasite/Solosite gel®, which contains propylene glycol
  - Add lidocaine to reduce burning discomfort or change base
- Propylene glycol has been reported to be a potential irritant and sensitizing agent in a small number of patients

NHA Foundation 2012: Use of topical morphine

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Challenges/Future Concerns

- Expanding use of topical opioid by other services (wound care, plastic surgery)
- Inpatient and outpatient pharmacy keeping up with patient/service demand—need to outsource compounding
- When patient discharged (home or LTAC), will their insurance cover the topical opioid, and who will supply compounded medication?

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References

- Carnel SB, Blakesless DB, Oswald SG, Barnes M. Treatment of radiation and chemotherapy-induced stomatitis. Otolaryngol Head Neck Surg. 1990; 102:326-30.
- Cerchietti LC, Navigante AH, Bonomi MR et al. Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. Cancer. 2002; 95:2230-2236. Note: Erratum published in Cancer 2003; 97(4):1137. DOI: 10.1002/cncr.11257.
- Gallagher RE, Arndt DR, Hunt K. Analgesic effects of topical methadone; a report of four cases. Clin J Pain. 2005;21:190-192.
- Picard PR, Tramer MR, McQuay HJ et al. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomized controlled trials. Pain. 1997; 72:309-318.
- Poonawala T, Levay-young BK, Hebbel RP, Gupta K. Opioids heal ischemic wounds in the rat. Wound Repair Regen. 2005; 13:165-74.
- Porzio G, Marchetti P. Topical morphine in the treatment of painful ulcers. J Pain Symptom Manage. 2005; 30:304-305.
- Twillman RK, Long TD, Cathers TA. Treatment of painful skin ulcers with topical opioids. J Pain Symptom Manage. 1999; 17:288-292.
- Vernassiere C, Cornet C, Trechot P et al. Study to determine the efficacy of topical morphine on painful chronic skin ulcers. J Wound Care. 2005; 14:289-93.

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References (cont'd)

- Zeppetella G, Paul J, Ribeiro MDC. Analgesic efficacy of morphine applied topically to painful ulcers. J Pain Symptom Manage. 2003; 25:555-558.
- Zeppetella G, Joel SP, Ribeiro MD. Stability of morphine sulphate and diamorphine hydrochloride in intrasite gel. Palliat Med. 2005; 19:131-6.
- Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. J Pain Symptom Manage. 2005; 29:118-119.
- Reddy M, Keast D, Fowler E, Sibbald RG. Pain in pressure ulcers. Ostomy Wound Manage 2003; 49(4 Suppl):30 –35.
- Uzaraga I, Gerbis B, Holwerda E, et al. Topical amitriptyline, ketamine, and lidocaine in neuropathic pain caused by radiation skin reaction: a pilot study. Support Care Cancer 2012; 20:1515 –1524.
- Tan T, Barry P, Reken S, Baker M, Guideline Development Group. Pharmacological management of neuropathic pain in nonspecialist settings: summary of NICE guidance. BMJ 2010; 340:707– 709.
- Graham T, Grocott P, Probst S, et al. How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. Pain. 2013; 154 (10): 1920–1928.
- Watterson G et al. Peripheral opioids in inflammatory pain. Arch Dis Child 2004; 89: 697–681.
- Twillman RK et al. Treatment of painful skin ulcers with topical opioids. J Pain Symptom Manage 1999; 17: 288–292.

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