



National Hospice and Palliative Care Organization
Palliative Care Resource Series

**DIFFERENTIATING MYTHS FROM
SUITABLE APPROACHES TO MEDICATION
MANAGEMENT IN HOME-BASED
PALLIATIVE CARE**

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MEDICATION MANAGEMENT IN HOME BASED PALLIATIVE CARE: THE NEED

Palliative care specialists are continually searching for alternative methods to safely and effectively administer medications that would allow for patients to remain in the home setting. This is coincided by a desire to preserve optimal symptom management, achieve goals of care, and avoid the burden of hospital admissions.

Knowledge of the misconceptions surrounding medication management in this patient population is important to ensure progress towards symptom control while maintaining patient safety. This paper will describe common myths associated with medication management in palliative care and hospice populations and offer effective, real strategies for medication management. This paper will also provide strategies for home based medication management and the use of off label medications in the home setting.

COMMON MYTHS ASSOCIATED WITH MEDICATION MANAGEMENT IN THE PALLIATIVE CARE AND HOSPICE POPULATIONS

Myth: Most seriously ill patients prescribed opioids can be classified as “opioid-tolerant”

Reality: It is a common misconception that most seriously ill patients, particularly those who are nearing the end of life, are able to tolerate potent or high doses of opioids upon initiation of therapy.

- Opioid tolerance is defined as receiving the following for 1 week or longer:
 - 60mg of oral morphine daily,
 - 25mcg of transdermal fentanyl per hour,
 - 30mg of oral oxycodone daily,
 - 8mg of oral hydromorphone daily,
 - 25mg of oral oxymorphone daily, or
 - An equianalgesic dose of another opioid
- No matter the patient status, a comprehensive medication history should be performed to discern exposure to opioid therapy for the treatment of pain or shortness of breath. If a patient does not meet the above criteria for being opioid tolerant, the dosing approach should be similar to that for a new start opioid naïve patient.
- Depending upon the patient’s age and clinical status, including the presence of organ failure, there may be consideration for a more conservative approach to initial opioid dosing in comparison to a younger, healthier opioid-naïve adult.

Myth: Opioids are effective as monotherapy for purely neuropathic pain syndromes

Reality: An appropriate baseline diagnosis with a differential should always be performed to provide insight regarding the biological mechanism(s) of the existing pain syndrome(s). This will allow for analgesics to be chosen with a mechanism of action that targets the identified condition(s).

- None of the current treatment guidelines focused on the treatment of neuropathic pain syndromes recommend opioid therapy as a first line class of medications due to lack of

effectiveness as monotherapy. Instead, these guidelines recommend an initial trial of analgesics with mechanisms of action that target serotonin and norepinephrine inhibition, such as antidepressants, or those that suppress neuronal hyperexcitability, such as anti-convulsants.

- Examples of analgesics and dosing strategies for the treatment of neuropathic pain include:

Gabapentin: Anticonvulsant, GABA analog

Initial → 100mg PO daily to TID (adjust for renal function)

May titrate dose every 1-3 days based upon patient tolerability to adverse effects, such as drowsiness/sedation

Usual effective dose 900-1800mg/day

Amitriptyline: Tricyclic antidepressant (TCA), tertiary amine

Initial → 10-25mg PO nightly; titrate every 4-7 days

May take days to weeks to receive analgesic benefit

Anticipate anti-cholinergic adverse effects and risk for cardiac toxicity

Secondary amine TCAs, such as nortriptyline, have ↓ risk for anticholinergic adverse effects and may be a more ideal alternative in the elderly population

Duloxetine: Serotonin/norepinephrine reuptake inhibitor (SNRI)

Initial → 30mg PO once daily for 1 week, then increase to 60mg once daily as tolerated

Doses up to 120mg/day were studied in clinical trials, but did not confer any additional benefit

Better tolerated, lower tendency for drug-drug interactions, and better overdose safety vs. TCAs

- Opioids have been shown to be beneficial as adjunctive therapy to these first line agents, but should not be used alone to optimize pain control for purely neuropathic pain syndromes.

Myth: Multiple product-containing topical compounds are effective for the treatment of systemic symptoms away from the site of application (e.g. nausea)

Reality: Localized topical administration of medication does NOT achieve high enough serum concentrations to impact symptoms in locations away from the site of application.

- Typically, serum levels of topically applied compounds are insignificant. With local administration of a topical compound, achieving high bioavailability can be challenging. Tissue penetration is dependent upon molecular size and physiochemical properties of the agent.
- Topical administration of medications is beneficial because systemic side effects are unlikely, but the capability to treat symptoms that are NOT localized, such as nausea or pain away from the site of application, is inadequate.

Myth: Benzodiazepines are first line for the treatment of delirium

Reality: Medication effects are a common cause of delirium both in the general population and in patients near the end of life. The goal of pharmacologic treatment of delirium should be to bring patients closer to their baseline mental state, not to sedate them or to suppress agitation.

- While benzodiazepines may have some benefit initially, this class of medications has the opportunity to contribute to excess sedation, particularly at the large doses that are commonly required to control symptoms. At these high doses, there is also risk for paradoxical reactions, such as irritability, which can worsen delirium and limit their being an ideal first line option.
- Neuroleptics, such as haloperidol, are commonly used as first line pharmacologic therapy for the treatment of delirium and are dose adjusted based upon severity of symptoms.
- If the goals of care include a desire to sedate the patient to provide relief in the presence of intractable/refractory suffering at the end of life, the use of benzodiazepines is more ideal.
- Other indications for which benzodiazepines have a role in therapy at the end of life include anxiety, seizures, insomnia, and muscle spasms.
- To reduce the opportunity for adverse effects related to benzodiazepines in the elderly, frail or cirrhotic patient populations, consider the use of agents with no active metabolites, such as lorazepam, oxazepam and temezepam (LOT).

Myth: Megestrol acetate is associated with significant, meaningful weight gain in all patient populations

Reality: Megestrol is included in the 2015 Updated Beer’s Criteria for Potentially Inappropriate Medication Use in Older Adults.

- Data does not support the use of megestrol for weight gain. The increase in weight tends to be minimal and mostly fat instead of lean body mass. Also, this agent is associated with increased risk of thrombotic events, such as deep vein thrombosis, and possibly death in older adults.
- Megestrol is currently FDA approved for the following indications: anorexia or cachexia associated with AIDS, breast cancer, advanced and endometrial cancer, advanced. It is also utilized off-label for cancer-related cachexia.
- The risk versus benefit of this agent for appetite stimulation, particularly for indications that are NOT FDA approved, should be evaluated.
- Risk of use may outweigh the benefit for those patients with a significant past medical history that may contribute to increased risk for one of these potential adverse effects (e.g. significant cardiac or thromboembolic history).
- Alternatives for weight gain/improved appetite that may be considered include dronabinol, mirtazapine or dexamethasone.

Myth: Anticoagulant therapy should be discontinued for all patients transitioned to hospice care

Reality: Despite a patient being transitioned to hospice care, there may remain greater than or equal to 6 months of life, during which time the need for anticoagulant therapy should be reevaluated based upon the patient’s clinical status.

- The risk of a thrombosis event should be weighed against the risk of bleeding when deciding whether anticoagulant therapy should be continued. For example, a patient who recently experienced an acute thrombosis event, such as a pulmonary embolism, who has active cancer, may be considered safer if anticoagulant therapy is continued due to the risk for recurrent thrombosis that can be fatal.
- On the other hand, a patient with a history of atrial fibrillation with a low risk for stroke may be at a greater risk for bleeding if anticoagulation is continued, particularly as prognosis worsens or patient nears death.

- The CHA2DS2-VASc stroke risk assessment tool can be used in patients with a history of atrial fibrillation to assist in predicting patients at high risk and truly low risk for stroke. The higher the CHA2DS2-VASc score, the greater the risk for stroke in the absence of thromboprophylaxis.

Risk Factor	Points
C - Congestive Heart Failure	1
H - Hypertension	1
A - Age > 75 years	2
D - Diabetes Mellitus	1
S - Prior Stroke/TIA/thromboembolism	2
V - Vascular Disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A - Age 65-74 years	1
Sc - Sex category (female)	1

- Acute or significant changes in clinical status, such as reduction in appetite, or concern for organ dysfunction, may warrant reassessment for risk versus benefit of continuation of therapy. This is particularly for patients prescribed warfarin therapy due to the opportunity for these changes to impact requirements to maintain INR stable within therapeutic range. It would be encouraged to monitor the INR more closely, as often as a weekly to biweekly basis to determine need for dose adjustments.
- Clinical judgment should be utilized on a patient by patient basis to determine the optimal treatment course. To optimize comfort for patients receiving hospice care, continual focus on goals of care and reevaluation of benefits and burdens of maintenance medications should be performed.

Myth: The intramuscular (IM) route of administration is an optimal alternative in the absence of oral and intravenous access

Reality: The American Pain Society recommends against the use of the intramuscular (IM) route for the treatment of pain due to its multiple disadvantages, including painful injections (“causing pain to treat pain”), unreliable absorption that may make it difficult to maintain consistent blood levels and risk for tissue damage/fibrosis with chronic IM injections.

- There are a variety of other more ideal routes of administration that can be utilized in the absence of oral or IV access which are reviewed in the below section focused on unique routes of medication administration.

Myth: Long acting analgesics can safely be titrated for the treatment of acute pain syndromes (e.g. fentanyl patch)

Reality: Acute pain cannot be optimized in a short period of time by a long acting agent since this formation cannot be titrated frequently enough to avoid adverse effects and maintain patient safety.

- It takes four to five half-lives to achieve serum steady state concentrations and to see the full effect of a particular dosing schedule. If a medication is titrated prior to achieving steady state concentrations, there remains opportunity for accumulation in the patient's system and increased risk for adverse effects.
- For example, use of a fentanyl patch to treat acute pain is NOT recommended, since it takes up to ~12 hours for systemic absorption after initial application and it may take several days before the full effect of a dose is apparent. Attempting to titrate the fentanyl patch more frequently than every 3-6 days can significantly increase a patient's risk for adverse effects, including respiratory depression and opioid overdose death.
- In an attempt to optimize acute pain control, the use of immediate release analgesics should be utilized to allow for rapid onset of action and frequent titration.

UNIQUE ROUTES OF MEDICATION ADMINISTRATION UTILIZED IN THE HOME

There are unique strategies to home-based medication management that have been found to be beneficial. The oral route of administration is preferred for medication administration, but is not always available due to reasons, such as, inability to swallow, persistent nausea/vomiting, severe oral lesions, weakness, unconsciousness/sedation or bowel obstruction.

The World Health Organization published a list of medications that are classified as "essential" in palliative care to prevent and relieve suffering based upon the most common symptoms in this patient population, such as anorexia, anxiety, constipation, delirium, depression, diarrhea, fatigue, nausea/vomiting, pain and respiratory tract secretions.

The medications recommended to treat these symptoms include benzodiazepines, haloperidol, laxatives, metoclopramide, opioid analgesics, steroids, anti-depressants, and anti-cholinergic agents. In the absence of oral access, there are a variety of methods that can be utilized to administer these medications to help maintain symptom control.

Alternative Routes of Administration

Routes	Medication Classes/ Formulations	Considerations
Enteral tube feeding	Long acting opioids (e.g. methadone solution, Kadian, Xtampza); any agent that can be crushed or opened and contents poured	<ul style="list-style-type: none"> ■ Provides alternative for bypassing gastroesophageal obstructions ■ Delivers medications to stomach or upper intestine ■ Whole capsules/tablets should NOT be placed in feeding tube ■ Concomitant administration of medications with tube feedings may have a significant impact on medication absorption ■ <u>Common agents impacted:</u> fluoroquinolones, antacids, phenytoin, theophylline, warfarin, and sucralfate ■ To avoid impacting medication absorption, recommend to HOLD the tube feedings for 2h before and 2h after medication administration
Inhaled	Opioids (e.g. morphine, fentanyl), local anesthetics (e.g. lidocaine, bupivacaine), diuretics (e.g. furosemide), saline solution	<ul style="list-style-type: none"> ■ Administered via nebulizer ■ Can be used for treatment of dyspnea, or cough ■ Low cost ■ Nebulized opioids may provide no additional benefit vs. saline solution for treatment of dyspnea
Intranasal	Manufactured and compounded products (e.g. butorphanol, fentanyl, ketamine, ketorolac, lidocaine, midazolam, naloxone, triptans)	<ul style="list-style-type: none"> ■ Bypasses liver/first pass metabolism ■ Absorption is rapid with serum levels and rate of absorption comparable to IV administration ■ Most effective with lipophilic, low molecular weight drugs ■ Dose ~1.5-2 times the parenteral dose ■ Use highly concentrated products ■ Ideal volume is less than 0.3ml/nostril ■ Do not exceed 1mL/nostril ■ If more than 2mL is needed, consider 2nd dose in 10 minutes ■ Expensive
Rectal	Manufactured and compounded suppositories (e.g. morphine, hydromorphone, diazepam, acetaminophen, indomethacin, promethazine, prochlorperazine); oral tablets (off-label)	<ul style="list-style-type: none"> ■ 1:1 conversion PO: rectal ■ Suppository dosing interval is typically every 4 to 6 hours ■ Degree of absorption may be impacted by: <ul style="list-style-type: none"> ■ Placement of the suppository → lower placement, ↓ hepatic first pass metabolism ■ Inter-individual variability ■ Expulsion ■ Administration of ER oral tablets is NOT FDA approved ■ Almost any pill taken orally can be given rectally ■ Absorption may be inadequate or variable ■ Absorption may be delayed if stool prevents contact with rectal mucosa or drug lost due to defecation ■ Drugs NOT well absorbed rectally: azithromycin, gabapentin, phenytoin, levetiracetam ■ Avoid enteric coated tablets due to requiring acidic environment for absorption ■ Route may not be accessible in the setting of diarrhea, constipation, fecal impaction, fissure or in the presence of patient/caregiver unacceptability

Alternative Routes of Administration (continued)

<p>Subcut</p>	<p>Opioids, benzodiazepines, anti-emetics, anti-psychotics, anti-cholinergics</p>	<ul style="list-style-type: none"> ■ Easy access/no need to find a vein ■ Reduced risk of infection vs. IV ■ Can administer intermittent injections or by continuous infusion ■ 1:1 conversion IV infusion: Subcut infusion ■ Delayed onset/offset of action vs. IV ■ Can administer patient controlled analgesia (PCA) via this route ■ Rate limitations → ~3-5ml/hour per site ■ Subcut tissue in the abdomen can be used for fluid hydration (e.g. hypodermoclysis) as abdominal skin can accommodate a higher volume ■ Rotate access site every 7 days unless a high volume is infused, or local skin irritation, itching, site bleeding or infection occurs ■ Some agents can be highly irritating and may require more frequent site changes (e.g. haloperidol, methadone, phenobarbital) ■ Unsatisfactory in the presence of anasarca, coagulopathy, circulatory insufficiency or in the presence of caregiver unwillingness to administer an injection
<p>Topical</p>	<p>Manufactured and compounded analgesic and anti-inflammatory medications (e.g. diclofenac, lidocaine)</p>	<ul style="list-style-type: none"> ■ Target peripherally located sites of pain ■ Typically applied directly over the painful site ■ Insignificant systemic activity ■ Consider avoiding topical compounds containing multiple agents ■ Expensive ■ Lack of literature supporting benefit /variable absorption depending upon lipophilicity of the components added ■ Consider using one drug at a time to identify beneficial therapies
<p>Transdermal</p>	<p>Analgesic patches (e.g. fentanyl, buprenorphine), anti-cholinergic patch (e.g. scopolamine)</p>	<ul style="list-style-type: none"> ■ Ideal for patients unable to take PO medication or who will pull out IV/Subcut catheter ■ Serum levels are necessary for pharmacodynamic effect ■ Has systemic activity ■ Can be applied in a location away from the site of action and still provide benefit for symptom management ■ Absorption may be increased in the presence of fever or exposure to heating sources, e.g. electric blanket, heating pad ■ Pharmacokinetics or clearance may be altered in elderly, cachectic or debilitated patients that increases likelihood of respiratory depression with opioid patches
<p>Transmucosal (buccal/sublingual)</p>	<p>Concentrated oral solutions (e.g. lorazepam, morphine, oxycodone, methadone)</p>	<ul style="list-style-type: none"> ■ For patients unable to swallow or who are dying ■ Can be scheduled around the clock to provide baseline pain relief ■ Limit volume to 1mL per dose ■ Volume limitations may impact usefulness to optimize pain control for patients with moderate to high opioid requirements ■ Absorption is dependent on lipophilicity of the agent (↑ lipophilicity, ↑ absorption), e.g. hydrophilic agents = morphine, oxycodone; lipophilic agents = fentanyl, methadone ■ Solution must be retained in sublingual space and absorbed to avoid first pass metabolism ■ Some or all of the medication may be swallowed if not adequately absorbed ■ Absorption may be hindered in the presence of copious secretions ■ In presence of diminished consciousness, may be increased risk for aspiration ■ Non-invasive/low cost

OFF-LABEL USE OF MEDICATIONS FOR SYMPTOM TREATMENT IN THE HOME SETTING

Several of the essential medications that are used within the palliative care/hospice patient population are NOT FDA approved for certain indications despite having literature and clinical consensus support for use. It is important to gauge how to safely and effectively utilize these medications.

Indication (Off-label)	Agent	Typical Dosing	Caveats/Considerations
Analgesia	dexamethasone	2-20mg PO/Subcut/IV daily	<ul style="list-style-type: none"> Long half- life (>36 hours) Less frequent dosing Commonly utilized for bone pain due to metastases, compression or pathological fractures
	ketamine	<p>Parenteral (Subcut/IV): A trial of 5-10mg can be considered</p> <p>CI: Initial - 0.1-0.2mg/kg/h <ul style="list-style-type: none"> Should not titrate for 1h following initiation Titration - ↑ by 0.1mg/kg/h q1-6h Max - 0.5mg/kg/h </p> <p>Intermittent: 0.1–0.5 mg/kg as a slow bolus administered over at least 30 min</p> <p>Oral: Initial - 10-20mg q6-8h <ul style="list-style-type: none"> Titration - ↑ daily by 10-20mg q6h until pain relieved or side effects occur </p>	<ul style="list-style-type: none"> Dosing based upon ideal body weight Consider conservative dosing in the presence of organ dysfunction Insufficient data for use in impaired liver function Psycho-cognitive effects are dose-related (Esp. at doses >2mg/kg; minimal at infusion rates less than 2.5mcg/kg/min) Consider pre-medication with benzodiazepine (↓ incidence of psychosis by 50%) Can reduce morphine tolerance Consider decreasing long acting opioid by 25-50% (& continue to taper based upon analgesia/sedation) Consider co-prescribing glycopyrrolate PRN for excessive salivation/lacrimation Consider co-prescribing clonidine or other anti-hypertensive agent for ↑ blood pressure Due to concerns around urinary tract toxicity, consider using ketamine long-term only if a “burst” approach has failed Duration of benefit varies No commercially available oral product Injected product may be diluted with cherry syrup or cola to mask bitter taste
Anorexia/ appetite stimulation	mirtazapine	7.5mg-15mg PO QHS	<ul style="list-style-type: none"> Associated with increased appetite and unintentional weight gain in patients treated for depression Lower doses are more sedating (< 15mg) Higher doses are more energizing (>30mg); administer in the AM
	dexamethasone	1-4mg/day PO/ Subcut/IV <ul style="list-style-type: none"> Consider taper to discontinuation after 2 weeks 	<ul style="list-style-type: none"> Meta-analysis shows benefit in adult patients with a diagnosis of anorexia-cachexia related to cancer May provide only temporary improvement in appetite; effects on body weight unclear May be beneficial in patients with poor prognosis (<4-6 weeks)

(continued)

Depression	ketamine	0.5mg/kg PO QHS	<ul style="list-style-type: none">■ Onset rapid, 1-3 days■ Although effect of single dose can last weeks, often dosed nightly■ May need to titrate if effects wear off■ Use with caution in patients with dementia or psychosis
	methylphenidate	5mg PO q 0800 and noon	<ul style="list-style-type: none">■ Rapid onset of action, 1-3 days■ May be used concurrently with SSRIs
Fatigue	dexamethasone	1-2mg PO daily	<ul style="list-style-type: none">■ Low dose may provide modest improvement for a short time, 2-4 days
	methylphenidate	5mg PO twice daily (0800 & 1300); ■ Increased based upon tolerability in increments of 10mg/day every 3 days up to a max of 40mg/day; ■ If no improvement in 7 days, discontinue	<ul style="list-style-type: none">■ Rapidly effective, often 1-2 days■ Usually well tolerated
Hiccups	baclofen	Initial - 5mg PO TID	<ul style="list-style-type: none">■ Try one agent at a time for up to 10 days■ If effective, continue x 24 hours after cessation of hiccups
	haloperidol	Initial - 1-4mg PO/Subcut/IV TID	
	metoclopramide	Initial - 10mg PO/Subcut/IV qAC and HS	
Malignant bowel obstruction	octreotide	Initial - 100-300mcg Subcut/IV q8h	<ul style="list-style-type: none">■ Decreases intraluminal secretions and peristalsis
Mucositis	ketamine rinse	20mg injectable ketamine mixed in 10ml cherry syrup, swish 2 min and spit, q3h PRN	<ul style="list-style-type: none">■ If unable to swish topical suspensions, medication can be applied via an oral swab
	morphine 20mg/ml rinse	Mix 0.1mL in 10mL water; swish for 2min, q3h PRN	
Nausea/vomiting	dexamethasone	2-20mg PO/Subcut/IV qAM; if dose is divided, give second dose early in the day	<ul style="list-style-type: none">■ Improves efficacy of 5HT3 anti-emetics in chemotherapy
	haloperidol	1.5-3mg/day; titrate daily based on response and tolerability up to a maximum of 6mg per 24hr	<ul style="list-style-type: none">■ Can be administered as a low dose continuous subcutaneous infusion
	metoclopramide	10-20mg PO/Subcut/IV q4-6h	<ul style="list-style-type: none">■ Up to 40mg for chemo-induced N/V
Shortness of breath	opioids	Dosing approach consistent with that for analgesia	<ul style="list-style-type: none">■ Opioid requirements for dyspnea are not typically as high as that warranted for analgesia
Terminal secretions	glycopyrrolate	Initial - 0.2mg PO/Subcut/IV q4h PRN ■ May titrate up to 0.8mg q4h	<ul style="list-style-type: none">■ May also be given by continuous IV/subcut infusion■ Does not cross blood brain barrier
	hyoscyamine	Initial - 0.125-0.25mg PO/SL q4h PRN ■ Titrate up to q30min PRN	<ul style="list-style-type: none">■ Max 1.5mg/day■ Available as orally disintegrating tablet and oral elixir/solution formulations

AC = before meals, CI= continuous infusion, IV= intravenous, N/V = nausea/vomiting, PO = oral, QHS = every night at bedtime, Subcut = subcutaneous

SUMMARY: LESSONS LEARNED AND BEST PRACTICES

There are a variety of viable alternative routes of medication administration to facilitate symptom management in the home-based setting. It is important to always take into consideration the manufactured formulation and pharmacokinetic profile of the medication to discern whether it is practical to administer via an alternative route. For assistance with unique medication formulations, identify your local compounding pharmacy to inquire regarding feasibility of medication preparation.

Additionally, there are medications that are utilized off-label in the home-based setting for the treatment of symptoms at the end of life. It is important that use of these agents is approached in a safe and effective manner that is consistent with existing literature. As can be noted above, several medications have a dual mechanism of action that can target one or more symptoms. This can facilitate streamlining the medication regimen and reduce pill burden.

In conclusion, clinicians should be knowledgeable of the strategies available to facilitate medication management in the home-based setting to help maintain patient comfort and achieve goals of care. Medications can help to assist with optimizing quality of life for a patient while being able to remain in their home and reduce the likelihood of hospitalization secondary to lack of knowledge regarding alternative approaches to care.

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