Orodispersible and transmucosal alternative medications for symptom control in adults

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ABSTRACT

Background Paediatric palliative care makes frequent use of orodispersible and transmucosal drug delivery routes. The limited published experience of this practice suggests that it enables the delivery of needle-free symptom relief, with the potential to train family carers to administer anticipatory medications without reliance on trained health professionals.

Aims To identify orodispersible and potential transmucosal alternatives that may be used in adults in the event of a patient having no oral or intravenous route and no access to subcutaneous injections.

Methods The author panel identified medications through review of multiple drug formularies, review of the published evidence and their experience. Where possible, licensed alternatives were identified and any 'off label' or unlicensed medications clearly highlighted.

Results A list of 27 medications is provided, which could be used either via the orodispersible or transmucosal alternative route for healthcare professionals delivering end of life care to consider when the licensed alternative routes are unavailable. All users of this guide are encouraged to use their professional judgement whenever selecting a medication for a patient, recognising that this review is neither a guideline nor a systematic review, and taking account of licensing considerations, adverse effects, potential unpredictability of time to effect and contraindications.

Conclusion Should it be necessary to use these orodispersible or transmucosal alternatives then any experience gained should be reported in the literature. Combined with further research, this experience offers the possibility of reducing injection frequency and inherent delays in medication administration, particularly in the community setting during the COVID-19 pandemic.

AIM

Our aim in writing this guide is to provide a resource from which healthcare professionals can select medications to control symptoms when patients do not have an oral route and when injectable medications are not available. This will enable high-quality needle-free palliative care, particularly in the community. We aim to summarise the evidence available regarding the transmucosal route, how transmucosal medications are administered, why they are effective and how transmucosal medications might be integrated into clinical practice.

BACKGROUND

Transmucosal drug administration uses the mucous membranes to deliver medication and is particularly beneficial when a patient cannot swallow tablets or liquids but does not have access to injectable medications or where the patient prefers to avoid injections. The mucosal membranes absorb lipophilic drugs rapidly, minimising first pass metabolism and therefore frequently leading to a rapid onset of effect. For these reasons, transmucosal drug administration lends itself to use for rapid management of breakthrough symptoms.[1] The utilisation of transmucosal routes of administration is widely established in paediatrics.[2]

Prior to consideration of the transmucosal route, it is important that every effort is made to use other available routes. In particular, it is important to consider alternative formulations, such as liquids in order to optimise the oral route before switching to a transmucosal alternative.

Examples of medications licenced and commonly used in the adult palliative population, which use the transmucosal route include nasal administration of

Table 1 Alfentanil buccal, sublingual or nasal

Alfentanil buccal, sublingual or nasal	
What is it?	Strong opioid analgesic—CD schedule 2 drug
Mechanism of action	Opioid having central agonist effect
Dose	10%–16% of the total CSCI dose hourly prn
Time to onset of effect	5 min[17]
Formulation	Nasal spray with attachment for buccal/SL use (5 mg/5 mL) bottle available as special order from Torbay Hospital Manufacturing Unit Tel: 01803 664 707. Each 'spray' delivers 0.14 mL=140 µg alfentanil OR Injection preparation given via buccal, sublingual or nasal route. Two strengths available, 500 µg/mL and 5 mg/mL
Indication	Moderate to severe pain for the management of breakthrough, incident or procedural pain when eGFR <20
Common adverse effects	Apnoea; chills; fatigue; hypertension; movement disorders; muscle rigidity; procedural complications[16]
Contraindications	Avoid or use a reduced dose in hepatic failure[17]
Licencing	Nasal spray is an unlicensed product Injection is licensed but a transmucosal route is 'off label'
Benefits	Rapidity of onset of action Ease of nasal administration
Risks	Prescribing/administration error Lack of familiarity with drug Lay carer administration Lack of availability Cost Unrecognised hepatic failure
Cost	Special—price on application

CD - Controlled Drug

CSCI - continuous subcutaneous infusion; SL - sublingual; eGFR - estimated Glomerular Filtration Rate

Table 2 Atropine sublingual

Atropine sublingual	
What is it?	Anticholinergic
Mechanism of action	Non-selective antimuscarinic
Starting dose	Four drops (800 µg—1 mg as size of drop varies) of 1% eye drops 4 hourly prn sublingually
Time to onset of effect	Uncertain (half-life 2–2.5 hours)[17]
Formulation	1% eye drops
Indication	Sialorrhoea Noisy rattling breathing
Common adverse effects	Constipation; dizziness; drowsiness; dry mouth; dyspepsia; flushing; headache; nausea; palpitations; skin reactions; tachycardia; urinary disorders; vision disorders; vomiting[16]
Contraindications	Acute myocardial infarction; arrhythmias; autonomic neuropathy; cardiac insufficiency; cardiac surgery; diarrhoea; elderly; gastro-oesophageal reflux disease; hypertension; hyperthyroidism; narrow angle-closure glaucoma; ileus; prostatic hyperplasia; fever; ulcerative colitis; myasthenia gravis[16]
Caution	Elderly
Licence	Unlicensed use and route for a licensed product
Benefits	Small volume Established body of use in palliative care practice
Risks	Varying dose with different droppers Systemic absorption
Cost	£131.89 for 10 mL 1% eye drops

fentanyl for pain; buccal administration of prochlorperazine for nausea and vomiting and rectal paracetamol for fever.

We defined methods of transmucosal drug administration as including buccal, sublingual, orodispersible, nasal and rectal routes. A prerequisite to the use of transmucosal medications is that the mucosal membrane must be moist. There are several important general principles for transmucosal drug administration, which include:

1. Only soluble drug molecules can be readily absorbed via mucosal membranes. Therefore, liquid preparations are preferable such as injection, concentrated solution or spray.
2. If chewable or orodispersible tablets are used, it is critical to ensure sufficient saliva is available to dissolve the tablets or alternatively tablets may be dissolved prior to administration. Buccal hydration may be improved by 2 hourly ice chips, Biotene oral gel or AS Orthna (contains porcine mucin).
3. To promote buccal or sublingual absorption keep the liquid in the mouth as long as possible without swallowing. Where the patient is not able to hold liquid in the mouth, the prescriber may choose to use a buccal tablet and gently massage the outside of the cheek following administration.
4. The bioavailability of drugs is likely to be higher via transmucosal route compared with oral route but lower than via parenteral routes. The effect of the drug will depend on how long it can be retained next to the mucosa and any gastrointestinal absorption if the drug is swallowed.
5. The need to supply the patient or caregiver with clear instructions on what each drug is being used for, how frequently it may be administered and how to administer

Table 3 Buprenorphine sublingual

Buprenorphine sublingual	
What is it?	Strong opioid analgesic
Mechanism of action	Opioid having agonist and antagonist properties
Starting dose	200 µg every 6–8 hours prn (equivalent to 15 mg morphine 6–8 hourly)
Time to onset of effect	10–20 min[17]
Formulation	Sublingual tablet—CD schedule three drug
Indication	Moderate to severe pain
Common adverse effects	Vomiting; opioid adverse effects; constipation; dizziness; drowsiness; dry mouth[16]
Contraindications	Acute respiratory depression, comatose, head injury, raised intracranial pressure[16]
Caution	Those at risk of aspiration Severe hepatic impairment
Licence	Temgesic and tephine are licensed products for pain
Benefits	May cause less constipation May cause less hyperalgesia
Risks	Systemic absorption Use complicated: advise patients that tablets should be dissolved under the tongue, not to swallow for 2 min and not to consume food or drink for at least 5 min after administration Non-registered carers will not be able to administer
Cost	£8.50 for 28×200 µg tablets

CD - Controlled Drug

Table 4 Carbamazepine rectal

Carbamazepine rectal	
What is it?	Analgesic—acting on neuropathic pain
Mechanism of action	Antiepileptic sodium channel blocker
Starting dose	125 mg two times per day
Time to onset of effect	4–8 hours[17]
Formulation	Suppository (125 mg rectally is approximately equivalent to 100 mg PO)
Indication	Neuropathic pain Seizures
Common adverse effects	Dizziness; drowsiness; dry mouth; eosinophilia; fatigue; fluid imbalance; gastrointestinal discomfort; headache; hyponatraemia; leucopenia; movement disorders; nausea; oedema; skin reactions; thrombocytopenia; vision disorders; vomiting; weight increased[16]
Contraindications	Acute porphyrias; AV conduction abnormalities (unless paced); history of bone marrow depression; cardiac disease; history of haematological reactions to other drugs may exacerbate absence and myoclonic seizures; skin reactions; susceptibility to angle-closure glaucoma[16]
Caution	Hepatic impairment Bone marrow suppression
Licence	Licensed product for seizure control; 'off label' for neuropathic pain
Benefits	Licensed product
Risks	Expensive Lack of familiarity with this use in palliative care
Cost	£120 for 5×125 mg suppositories

AV - atrial ventricular

Table 5 Cyclizine sublingual or rectal

Cyclizine sublingual or rectal	
What is it?	Antiemetic
Mechanism of action	Antihistaminic antimuscarinic antiemetic
Starting dose	50 mg two times to three times a day
Time to onset of effect	30–60 min[17]
Formulation	Injection given as a sublingual solution Rectal suppository (must be kept in fridge)
Indication	Nausea related to raised intracranial pressure Nausea-related gastrointestinal obstruction Nausea related to vestibular disorders
Common adverse effects	Anticholinergic adverse effects; movement disorders, potential for misuse/abuse of injections
Contraindications	Epilepsy; prostatic hypertrophy (in adults); pyloroduodenal obstruction; severe heart failure—may cause fall in cardiac output and associated increase in heart rate, mean arterial pressure and pulmonary wedge pressure; susceptibility to angle-closure glaucoma[16]
Caution	Renal and hepatic impairment
Licence	Use of injection orally: 'off label' Use of suppositories: unlicensed product
Benefits	Alternative routes of administration
Risks	Delay to manufacture of suppositories
Cost	Oral solution: 50 mg/mL ampoules for injection—£18.58 for 5 Suppository—a special order. Price of application

Table 6 Diazepam rectal

Diazepam rectal	
What is it?	Benzodiazepine
Mechanism of action	$GABA_A$ modulator
Starting dose	2.5 mg (approximately equivalent to 1.25 mg midazolam) 10 mg for seizure
Time to onset of effect	30 min[17]
Formulation	Rectal tube
Indication	Agitated delirium Anxiety Seizures
Common adverse effects	drowsiness; fatigue; muscle weakness; nausea; respiratory depression (particularly with high dose and intravenous use—facilities for its treatment are essential); sleep disorders; vertigo; vision disorders; withdrawal syndrome[16]
Contraindications	Coma; current alcohol abuse; current drug abuse; respiratory depression[16]
Caution	Hepatic impairment Renal failure
Licence	Licensed for anxiety and seizures; 'off label'for delirium
Benefits	Alternative route of administration
Risks	Greater evidence base with buccal midazolam than rectal diazepam
Cost	2.5 mg—£5.65 for 5 5 mg—£6.49 for 5 10 mg—£6.49 for 5

GABAA - gamma aminobutyric acid receptor type A

each drug to avoid any administration errors, as well as any adverse effects to be aware of.

6. Patients need to be monitored and assessed when switched to a transmucosal route and the dose adjusted as necessary.
7. It is best practice that injections prepared for sublingual or buccal administration are drawn up through a filter needle to reduce the risk of any glass injury to oral mucosa.

Furthermore, care needs to be taken to identify whether patients are swallowing or spitting out a large proportion of orally administered medications as this may further affect its efficacy. Taste is a particularly important factor as an unpleasant taste may make patients less likely to retain the medication on the buccal mucosa long enough for it to be effective. Anderson observed that:

'Buccal and sublingual administration, where there is considerable drug swallowed, results in lower plasma concentrations if that drug has a high first-pass effect because bioavailability is reduced'.[3]

In general, however, there is very limited pharmacokinetic and pharmacodynamic data available such as time to maximum concentration, time to maximum effect and half-life when using the mucosal route for off licensed drug administration. The lack of data regarding 'concentration–response relationship for either the beneficial or adverse effects'[3] of drugs means that adjustment of dose and frequency of

Table 7 Diamorphine intranasal or sublingual

Diamorphine intranasal or sublingual	
What is it?	Strong opioid - CD schedule 2
Mechanism of action	Mu agonist
Starting dose	1.25–2.5 mg 4 hourly prn (equivalent to 3.75–7.5 mg morphine PO)
Time to onset of effect	<5 min[17]
Formulation	Nasal spray (Ayendi(R)) OR Injection (powder for reconstitution) intranasal or sublingual routes
Indication	Moderate to severe pain
Common adverse effects	Vomiting; opioid adverse effects; constipation; dizziness; drowsiness; dry mouth[16]
Contraindications	Acute respiratory depression, comatose, head injury, raised intracranial pressure[16]
Caution	Those at risk of aspiration Severe hepatic and renal impairment
Licencing	Off license route of licensed injections Nasal spray (Ayendi(R)) licensed but not available in the UK at time of writing
Benefits	Rapidity of onset of action Ease of nasal administration
Risks	Prescribing/administration error Lack of familiarity with drug Lay carer administration and difficulty making up the drug
Cost	£12.81 for 5×5 mg ampoules for injection; Ayendi (R) price of application

CD - Controlled Drug

administration to maximise efficacy and yet minimise adverse effects is very challenging.

Furthermore, many orodispersible products must be swallowed in order to be fully absorbed as they are designed to ease oral administration, rather than to be directly absorbed across the mucosal membrane. It is therefore not clear whether they would be clinically effective if a patient was unable to swallow the tablet residue. The extent of transmucosal absorption will depend on the physiochemical properties of the drug molecules, specifically molecular size and lipophilicity. In general, drugs that can penetrate blood brain barrier to act on the central nervous system are likely to have reasonable transmucosal absorption.

Despite these caveats and considerations, transmucosal medications present the possibility of delivering needle-free symptom control, something which is routinely employed in paediatric palliative care because 'by and large, children hate needles'.[3]

Spathis and colleagues identified that this was an area of paediatric palliative care that had the potential to augment and enhance practice in adult palliative care:

'Family members can respond immediately to symptoms, without having to wait for the arrival of nursing

Table 8 Diclofenac rectal

Diclofenac rectal	
What is it?	Non-opioid analgesic
Mechanism of action	Non-steroidal anti-inflammatory selective Cox-2 inhibitor
Starting dose	50 mg 8–12 hourly prn
Time to onset of effect	30 min[17]
Formulation	Rectal suppository
Indication	Mild to moderate pain
Common adverse effects	Oedema; skin reactions; appetite decreased; diarrhoea; dizziness; gastrointestinal discomfort; gastrointestinal disorders; headache; nausea; rash (discontinue); vertigo; vomiting[16]
Contraindications	Allergy to aspirin, cardiovascular disease, gastrointestinal bleeding or history of perforation[16]
Caution	Hepatic impairment Renal failure[16]
Licence	Licensed
Benefits	Alternative route of administration
Risks	Difficult to administer
Cost	£1.24 for 10×25 mg or £2.04 for 10×50 mg suppositories

Table 9 Docusate rectal

Docusate rectal	
What is it?	Laxative
Mechanism of action	Faecal softener with some stimulant effect
Starting dose	120 mg
Time to onset of effect	30 min[17]
Formulation	Rectal enema
Indication	Constipation
Common adverse effects	Abdominal discomfort, anorectal irritation, incontinence[16]
Contraindications	Bowel perforation[16]
Caution	Proctitis Intestinal obstruction
Licence	Licenced
Benefits	Alternative route of administration
Risks	Difficult to administer
Cost	£28.00 for 6×120 mg enemas

Table 10 Domperidone orodispersible

Domperidone orodispersible	
What is it?	Antiemetic
Mechanism of action	Prokinetic D_2 antagonist
Starting dose	10 mg prn three times a day
Time to onset of effect	30 min([17])
Formulation	10 mg orodispersible tablets
Indication	Nausea and vomiting
Common adverse effects	Dry mouth; anxiety; asthenia; breast abnormalities; diarrhoea; drowsiness; headache; lactation disorders[16]
Contraindications	QT abnormality Prolactinoma[16]
Caution	Patients >60
Licence	Orodisperible tablet unlicensed product
Benefits	Alternative route of administration
Risks	Extrapyramidal adverse effects
Cost	Orodispersible tablet—special price of application

Table 11 Fentanyl nasal, buccal or sublingual

Fentanyl nasal, buccal or sublingual	
What is it?	Strong opioid (CD schedule 2)
Mechanism of action	Mu agonist
Starting Dose	50 (instanyl) to 100 mg (pecfent, abstral and efentora) A further 50 or 100 mg after 15–30 min if required Maximum two doses per pain episode Dose titration as per manufacturer's guidance
Time to onset of effect	15–20 min[17]
Formulation	Pecfent nasal spray Instanyl nasal spray Abstral sublingual tablet Effentora buccal tablet
Indication	Moderate to severe pain for the management of breakthrough, incident or procedural pain
Common adverse effects	Acute respiratory depression, comatose, head injury, raised intracranial pressure
Contraindications	Those at risk of aspiration
Licence	Licenced product
Benefits	Rapidity of onset of action Ease of nasal administration
Risks	Lack of familiarity with drug Lay carer administration Mucositis when using buccal or sublingual products
Cost	Abstral—£49.99 for 10×100 mg sublingual tablets; Effentora—£139.72 for 28×100 mg buccal tablets; Instanyl—£35.70 for 6× doses nasal spray 100 mg/dose; Pecfent—£36.48 for 8× doses nasal spray 100 mg/dose.

CD - Controlled Drug

Table 12 Glycopyrronium sublingual

Glycopyrronium sublingual	
What is it?	Antichloinergic
Mechanism of action	Antimuscarinic
Starting dose	200mcg eight hourly prn sublingual
Time to onset of effect	30–40 min[17]
Formulation	Oral solution OR Injection
Indication	Drooling Noisy rattling breathing Medical management of malignant bowel obstruction Paraneoplastic fevers and sweating
Common adverse effects	Constipation; dizziness; drowsiness; dry mouth; dyspepsia; flushing; headache; nausea; palpitations; skin reactions; tachycardia; urinary disorders; vision disorders; vomiting[16]
Contraindications	Tachycardia >100 Cardiac conduction disorders[16]
Caution	Elderly Renal impairment—may need to reduce dose
Licence	Oral solution 'off label' use in adults and 'off label' route (however licensed for oral administration in children>3 years to adolescents with neurological disorders) Injection is a licensed product but 'off label' route
Benefits	Small volume
Risks	Risk of glass ampoule when administering
Cost	£91 for 150 mL × 200 µg/mL oral solution £76.80 for 60 mL × 400 mcg/mL oral solution £9.95 for 10 × 200 µg/mL ampoules for injection

staff. This approach could be of considerable value in adult community palliative care practice'.[4]

The COVID-19 pandemic raised concerns that availability of district nurses in the community to administer medications via the traditional subcutaneous route for adults approaching the end of their lives may be outstripped by the steep increase in demand for their services. Additionally, there is a need to ensure that alternative medications are identified early so that this information is available to inform practice in the event of drug shortages.

CAUTION

All users of this guide are encouraged to use their professional judgement whenever selecting a transmucosal medication for a patient. The reader should note that this is neither a guideline nor a systematic review. Users must therefore consider their local and national guidelines as well as considering the evidence base for the drug they elect to use, its licencing, contraindications to its use and adverse events. Any statements regarding a drug's licencing are related to its use in the UK only and users are advised to check the relevant licencing requirements if they are practising in other countries around the world.

Table 13 Haloperidol buccal or sublingual

Haloperidol buccal or sublingual	
What is it?	Butyrophenone antipsychotic
Mechanism of action	D_2, alpha-adrenergic and sigma receptor antagonist
Starting dose	0.5 mg–1.5 mg 6–8 hourly
Time to onset of effect	I hour if give PO (buccal/sublingual may be faster)[17]
Formulation	Oral solution
Indication	Delirium Nausea and vomiting Hiccups Psychosis
Common adverse effects	Extra pyramidal effects, altered liver function tests, dizziness, sedation, visual disturbance, depression, hypotension[16]
Contraindications	Parkinson's disease, Lewy body dementia, cardiac disorders, QTc prolongation, recent myocardial infarction, decompensated heart failure heart failure[16]
Caution	Dementia, stroke risk, epilepsy, renal and hepatic impairment, cardiac disease[16]
Licence	Off licence use of licensed product
Benefits	Alternative route of administration of an antipsychotic
Risks	Time to effect unknown when used sublingually
Cost	*Price varies widely by product:* *£4.45 for 100 mL of Haldol* 2 mg/mL oral solution

Table 14 Hyoscine hydrobromide chewable

Hyoscine hydrobromide chewable	
What is it?	Antimuscarinic
Mechanism of action	Antisecretory with smooth muscle relaxant properties
Starting dose	150 µg 4 hourly prn
Time to onset of effect	10–15 min[17]
Formulation	Chewable tablets
Indication	Sialorrhoea Drooling Smooth muscle spasm Paraneoplastic fevers and sweating
Common Adverse Effects	Constipation; dizziness; drowsiness; dry mouth; dyspepsia; flushing; headache; nausea; palpitations; skin reactions; tachycardia; urinary disorders; vision disorders; vomiting[16]
Contraindications	Tachycardia >100 Cardiac conduction disorders[16]
Caution	Crosses blood brain barrier so may cause sedation Elderly Renal and hepatic impairment May prefer to use transdermal patch
Licence	'off label' use of a licensed product
Benefits	Chewable alternative
Risks	Aspiration
Cost	£1.67 for 12×150 mg Kwells £1.99 for 12×150 µg Joy-Rides tablet

METHODS

During the initial phase of the COVID-19 pandemic, local, regional and national symptom management guidelines were created.[5–15] These were hand searched to identify potential transmucosal alternatives that might be of use in the event of a patient having no oral or intravenous route and no access to subcutaneous injections.

Transmucosal alternatives are used in paediatric palliative care practice, both in the UK and internationally were explored. The experiences of expert

Table 15 Ibuprofen orodispersible or chewable capsule

Ibuprofen orodispersible or chewable capsule	
What is it?	Non-opioid analgesic
Mechanism of action	Non-steroidal anti-inflammatory non-selective Cox inhibitor
Starting dose	200 mg
Time to onset of effect	20–30 min onset[17]
Formulation	Orodispersible tablets or chewable capsule
Indication	Mild to moderate pain
Common adverse effects	Oedema; skin reactions; appetite decreased; diarrhoea; dizziness; gastrointestinal discomfort; gastrointestinal disorders; headache; nausea; rash (discontinue); vertigo; vomiting[16]
Contraindications	Allergy to aspirin or other NSAIDs, cardiovascular disease, gastrointestinal bleeding or history of perforation[16]
Caution	Hepatic impairment Renal failure
Licence	Licensed
Benefits	Licensed alternative route of administration
Risks	Worsening COVID-19, GI bleeding
Cost	£2.58 for 12×200 mg orodispersible tablets £3.23 for 12×100 mg chewable capsule

NSAIDs - non-steroidal anti-inflammatory drugs

Table 16 Ipratropium nasal

Ipratropium nasal	
What is it?	Antimuscarinic
Mechanism of action	Antisecretory with bronchodilator properties
Starting dose	41 µg (two sprays) 6–8 hourly prn
Time to onset of effect	15–30 min[17]
Formulation	Nasal spray
Indication	Rhinorrhoea Bronchial secretions Respiratory secretions
Common adverse effects	Dizziness; dry mouth; headache; urinary disorders; vision disorders; vomiting; tachycardia; GI dysmotility; oropharyngeal irritation; bronchoconstriction[16]
Contraindications	Tachycardia >100 Cardiac conduction disorders[16]
Caution	Narrow angle glaucoma Bladder outflow obstruction Cystic fibrosis
Licence	'off label' use of licensed product
Benefits	Easy to use
Risks	It is unknown whether sufficient systemic absorption is achieved via the intranasal route to improve bronchial and respiratory secretions
Cost	£6.54 for 180×21 µg/dose nasal spray

Table 17 Levomepromazine buccal or sublingual

Levomepromazine buccal or sublingual	
What is it?	Anti-psychotic
Mechanism of action	Central nervous system (CNS); receptors include adrenergic, dopamine, histamine, cholinergic and serotonin receptors
Starting dose	3 mg–25 mg once daily (or 6.25–12.5 mg as required maximum three times in 24 hours)
Time to onset of effect	Not known (30 min via oral route)[17]
Formulation	Oral tablet crushed, with water 6.25–25 mg; OR 6 mg tablets (Levinan) 3 mg (1/2 tablet) 4–6 hourly PRN (can be crush); OR injection 0.25–1 mL sublingual
Indication	Second line for nausea and vomiting or delirium and agitation
Common adverse effects	Postural hypotension; falls; 'asthenia; heat stroke'[16]
Contraindications	'CNS depression; comatose states; phaeochromocytoma'[16]
Caution	Dementia, cardiac, prolonged QT, Parkinsonism, hypothyroidism, seizure, postural hyotension, myasthenia, renal and liver impairment[16]
Licencing	Oral tablet licensed; Levinan is an unlicensed preparation available on a named patient basis; off licence route for injectable levoempromazine
Benefits	Buccal administration of broad spectrum, long acting anti-psychotic*
Risks	Injection concentration is 25 mg/mL so challenging to administer 0.25 mL, risk of injury from glass ampoule to lay carer
Cost	£20.26 for 84×25 mg tablets £20.13 for 10×25 mg/mL ampoules for injection; 6 mg tablets—special price of application

*Level of evidence supporting its use (CBEM): level 5; authors EH and ICKCW have clinical experience of its use.

Table 18 Loperamide orodispersible

Loperamide orodispersible	
What is it?	Anti-diarrheal agent
Mechanism of action	Opioid agonist effect on the large intestine
Starting dose	2–4 mg as needed maximum four times a day
Time to onset of effect	1 hour[17]
Formulation	Orodispersible tablets
Indication	Diarrhoea; colic
Common adverse effects	'Gastrointestinal disorders; headache; nausea'[16]
Contraindications	'Active ulcerative colitis; antibiotic-associated colitis; bacterial enterocolitis; conditions where abdominal distension develops; conditions where inhibition of peristalsis should be avoided'[16]
Caution	'Serious cardiovascular events (such as QT prolongation, torsades de pointes, and cardiac arrest)'[16]
Licencing	Licenced formulation
Benefits	A licenced orodispersible alternative for with good bioavailability in contrast to other alternatives such as hyoscine hydrobromide or glycopyrronium which have very low bioavailability when given via oral or buccal route
Risks	QT prolongation risk not yet widely recognised in clinical practice
Cost	£5.85 for 18×2 mg orodispersible tablets

colleagues working in a range of settings were sought, through both personal communication and published work.

Having identified potential therapeutic options, a list of alternative orodisperisible and transmucosal medications was reported and cross referenced with the British National Formulary (BNF), the Palliative Care Formulary (PCF) and the Association of Paediatric Palliative Care (APPM) Formulary and the Enteral Drug Handbook as appropriate.[16–19]

Table 19 Lorazepam sublingual

Lorazepam sublingual	
What is it?	Anxiolytic
Mechanism of action	Benzodiazepine
Starting dose	0.5–1 mg
Time to maximal effect	2.5 hours[17]
Formulation	Tablet—can be halved
Indication	Anxiety, panic, agitation
Common adverse effects	'Apnoea; asthenia; coma; disinhibition; extrapyramidal symptoms; hypothermia; memory loss; speech slurred; suicide attempt'[16]
Contraindications	Severe hepatic failure, untreated sleep apnoea, myasthenia gravis, severe respiratory failure[16]
Caution	'Avoid prolonged use (and abrupt withdrawal thereafter); debilitated patients (reduce dose) (in adults); elderly (reduce dose) (in adults); history of alcohol dependence or abuse; history of drug dependence or abuse; myasthenia gravis; personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence; respiratory disease'[16]
Licencing	Off license route of a licensed formulation
Benefits	Sublingual benzodiazepine, widely used in usual practice
Risks	Common misconception that the sublingual route is licensed due to widespread use
Cost	£3.29 for 28×1 mg tablets

Table 20 Miconazole buccal

Miconazole buccal	
What is it?	Azole anti-fungal
Mechanism of action	Disrupts the fungal cell member by inhibiting ergosterol synthesis
Starting dose	2.5 mL four times a day oral gel
Time to effect	Uncertain[17]
Formulation	Oral gel 'Oral gel should be held in mouth, after food' British National Formulary (BNF)
Indication	Oropharyngeal candidiasis
Common adverse effects	'Skin reactions…dry mouth; nausea; oral disorders; vomiting'[16]
Contraindications	Pregnancy due to teratogenicity
Caution	CYP3A4 inhibitor; 'Avoid in acute porphyrias'[16]
Licencing	Oral gel licenced and available to buy over the counter; [N.B. muco-adhesive buccal tablet is not yet listed in the BNF; muco-adhesive buccal tablet is not recommended by Scottish Medicines Consortium (SMC)*]
Benefits	Over the counter, simple administration, licensed product
Risks	Choking is listed as a side effect in children, adults with compromised swallow may therefore also be at risk of chocking, may not fully clear thrush if oesophageal involvement*
Cost	£4.38 for 80g×20 mg/g oromucosal gel

*Level of evidence supporting its use: "miconazole muco-adhesive buccal tablets were shown to be non-inferior to another locally acting miconazole preparation in the treatment of oropharyngeal candidiasis in patients with cancer of the head and neck who had received radiotherapy. There are no data comparing miconazole buccal tablets to treatments currently used in practice in NHS Scotland. The manufacturer did not present a sufficiently robust analysis to gain acceptance by Scottish Medicines Consortium (SMC). The licence holder has indicated their intention to resubmit." [21]

The potential list of transmucosal medications was discussed and reviewed by the author panel until consensus was achieved.

RESULTS

We identified 27 potential transmucosal alternative medications, listed below, and present the potential risks and benefits of each, their licensing status and costings, as listed in the BNF. We present an example table, see (tables 1–28).

DISCUSSION

Paediatric palliative has historically made greater use of oral transmucosal drug delivery for symptom relief in the community than adult palliative care. This practice offers an opportunity for rapid administration of needle-free symptom management in adults for whom transfer to hospital or hospice is not their preference or may be inappropriate, without delay inherent in subcutaneous medication administration by healthcare professionals in the community.

Use of licenced orodispersible medication in novel ways in adult palliative care via the transmucosal route

Table 21 Morphine rectal

Morphine rectal	
What is it?	Opioid analgesic
Mechanism of action	Mu opioid receptor antagonist
Starting dose	IR suppository 10 mg PR as required, maximum 2 hourly; conversion oral 1:rectal 1
Time to effect	45–60 min[17]
Formulation	Immediate release—suppositories are available as a specials order; when prescribing 'Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber.'[16] Modified release—Morphine MST Continus tablets given rectally
Indication	Moderate to severe pain, breathlessness
Common adverse effects	'Appetite decreased; asthenic conditions; gastrointestinal discomfort; insomnia; neuromuscular dysfunction'[16]
Contraindications	'Acute abdomen; delayed gastric emptying; heart failure secondary to chronic lung disease; phaeochromocytoma'[16]
Caution	See Direct.gov.uk for Drug Driving advice
Licencing	Suppository licensed; rectal use of modified release tablets is an off licence use
Benefits	A transmucosal alternative to oral or subcutaneous morphine
Risks	Unpredictability of bioavailability when rectal route used, 'Delayed absorption of rectal morphine has contributed to respiratory arrest in infants.'[3]
Cost	£19.45 for 12×10 mg suppositories; £5.20 for 60×10 mg modified release tablets

Table 22 Morphine sublingual

Morphine sublingual	
What is it?	Opioid analgesic
Mechanism of action	Mu opioid receptor antagonist
Starting dose	2.5 mg given as drops, up to hourly
Time to effect	Uncertain (16–60 min oral, but drug not lipophyllic therefore likely to be significantly longer)[17]
Formulation	20 mg/1 mL oral solution, designed for oral administration, risk of unpredictable absorption OR injection
Indication	Pain, breathlessness
Common adverse effects	'Appetite decreased; asthenic conditions; gastrointestinal discomfort; insomnia; neuromuscular dysfunction'[16]
Contraindications	'Acute abdomen; delayed gastric emptying; heart failure secondary to chronic lung disease; phaeochromocytoma'[16]
Caution	See Direct.gov.uk for Drug Driving advice
Licencing	'Off label' route of licensed oral solution; 'off label' route of licensed injection
Benefits	A transmucosal alternative to oral or subcutaneous morphine
Risks	Best avoided due to unpredictability of bioavailability when buccal route used, likely lower than oral due to solution not being lipophilic, likely no advantage over oral administration
Cost	£19.50 for 120 mL x 20 mg/mL oral solution; £11.47 for 10×10 mg/mL ampoules for injection

Table 23 Olanzapine orodispersible

Olanzapine orodispersible	
What is it?	Anti-psychotic
Mechanism of action	Antagonist to: D1, D2, D3, D4, 5HT(2A, 2C, 3, 6, 7), α1 and α2; anti-cholinergic
Starting dose	2.5 mg–10 mg prn ON initially, can be increased to BD
Time to onset of effect	Hours to days[17]
Formulation	Orodispersible tabs (placed on the tongue and allowed to dissolve, or can be dissolved in small volume water/juice)
Indication	Nausea and vomiting (low dose) or delirium and terminal agitation (higher dose)
Common adverse effects	'Anticholinergic syndrome; appetite increased; arthralgia; asthenia; eosinophilia; fever; glycosuria; oedema; sexual dysfunction'[16]
Contraindications	'Bone-marrow depression; hypereosinophilic disorders; low leucocyte count; low neutrophil count; myeloproliferative disease; paralytic ileus'[16] Narrow angle glaucoma[17]
Caution	Fatalities when injected due to over sedation or cardiorespiratory depression. Increased risk of this is coadministered with midazolam.
Licencing	'Off label' use of licensed drug if used for nausea and vomiting
Benefits	Improves mood, appetite, sleep as well as nausea and vomiting, and delirium*
Risks	Hyper somnolence, if used long-term patients will require blood monitoring—lipids, FBC, BM
Cost	£6.86 for 28×5 mg orodispersible tablets sugar free—those containing sugar are much more expensive

FBC - full blood count; BM blood glucose measurement

*Level of evidence supporting its use via the oral route as an anti-emetic in chemotherapy induced nausea and vomiting (CBEM): 1a (multiple meta-analyses) number needed to treat to benefit: 5; number needed to treat to harm: 19[22]

minimised the necessity to include other forms of 'off licence' or 'unlicensed' products in the list above. Healthcare professionals should use licensed medications by licensed routes in preference to 'off licence' or 'unlicensed' products wherever possible. However, situations may arise where, due to the nature of a patients' condition, symptom(s) or the complexity of the clinical situation (including drug and staff shortages), there are no licensed alternatives available. In these circumstances, it is necessary to 'give patients (or their carers) sufficient information about the medicines you propose to prescribe to allow them to make an informed decision', answering any 'questions from patients (or their carers) about medicines fully and honestly'.[20]

Therefore 'off licence' or 'unlicenced' alternatives have been included above where the author panel agreed that there is sufficient evidence, clinical experience or expertise of their use.

Reporting of learning from the experience in using transmucosal drugs in adult palliative care in the literature is encouraged to inform future practice. If combined with further research, this learning could

Table 24 Ondansetron orodispersible or rectal

Ondansetron orodispersible or rectal	
What is it?	Anti-emetic
Mechanism of action	Anti-serotonin 5HT3
Starting dose	Buccal 4 mg prn, max 16 mg in 24 hours; rectal 16 mg suppositories
Time to onset of effect	Uncertain (<30 min with oral route)[17]
Formulation	Orodispersible film 4 mg OR orodispersible tablets 4 mg 6–8 hourly PRN max 16 mg/24 hours OR 16 mg suppositories only dose available
Indication	Nausea and vomiting
Common adverse effects	'Constipation; feeling hot; headache; sensation abnormal'[16]
Contraindications	'Congenital long QT syndrome'[16] Serious drug interaction with metoclopramide due to combined QT prolongation effect[17]
Caution	May reduce efficacy of tramadol and paracetamol[17]
Licencing	Licensed formulation for an 'off label' indication in palliative care
Benefits	Licenced orodispersible and rectal alternative anti-emetic
Risks	Constipation, more costly than other alternatives such as olanzapine
Cost	£28.50 for 10×4 mg or £57 for 10×8 mg orodispersible films; £43.38 for 10×4 mg or £85.43 for 10×8 mg orodispersible tablets; £14.39 for 1×16 mg suppository

lead to long-term changes in clinical practice, perhaps reducing the need for subcutaneous medication administration in the community in future.

LIMITATIONS

Due to the COVID-19 pandemic and the urgent need to generate a list of transmucosal medications, there was insufficient time to undertake a rapid literature review of every medication listed above in order to establish an up to date evidence base for each.

It is outside the scope of this document to be able to offer guidance on the order of transmucosal drug selection to achieve symptom management, that is, which drug would be first, second or third line for any given symptom.

Table 25 Oxycodone sublingual

Oxycodone sublingual	
What is it?	Opioid analgesic
Mechanism of action	Mu opioid agonist
Starting dose	1.25–2.5 mg given as drops, maximum 1 hourly
Time to effect	Uncertain (20–30 min with oral route)[17]
Formulation	OxyNorm Concentrate 10 mg/mL oral solution
Indication	Pain, breathlessness
Common adverse effects	'Anxiety; bronchospasm; depression; diarrhoea; dyspnoea; gastrointestinal discomfort; hiccups; mood altered; tremor'[16]
Contraindications	'Acute abdomen; chronic constipation; cor pulmonale; delayed gastric emptying'[16]
Caution	See Direct.gov.uk for Drug Driving advice
Licencing	'Off label' route of licensed oral solution
Benefits	A transmucosal alternative to oral or subcutaneous morphine
Risks	Unpredictability of bioavailability when sublingual or buccal route used, likely lower than oral due to solution not being lipophilic
Cost	£46.63 for 120 mL × 10 mg/mL oral solution

Table 26 Paracetamol orodispersible or rectal

Paracetamol orodispersible or rectal	
What is it?	Non-opioid analgesic
Mechanism of action	Weak COX2 and peroxidase inhibitor
Starting dose	500 mg–1000 mg, maximum four times a day
Time to onset of effect	Uncertain (15–30 min with oral route)[17]
Formulation	Paracetamol FasTab 250 mg oradispersible tablets (2–4 tablets per dose, dependent on weight and liver function) Paracetamol suppositories 1 g; n.b. bioavailability is 60% compared with oral administration[3]
Indication	Pain, fever
Common adverse effects	Rectal 'anorectal erythema' with rectal preparation[16]
Contraindications	Severe liver dysfunction, 500 mg four times a day maximum if weight less than 50 kg
Caution	Old age, poor nutritional state, fasting, anorexia, weight <50 kg, chronic alcohol use[17]
Licencing	Both are licensed formulation
Benefits	Transmucosal alternatives for managing fever
Risks	Ensuring correct number of orodispersible are used; ensuring that dose is reduced to 500 mg four times a day if weight less than 50 kg or liver function tests severely deranged
Cost	£4.12 for 24×250 mg orodispersible tablets (Fastmelts—would need four tablets per 1 g dose); £59.50 for 10×1 g suppositories

Table 27 Prochlorperazine buccal

Prochlorperazine buccal	
What is it?	Anti-emetic
Mechanism of action	Antagonist to: D2, 5HT (2A and 2C), H1 and α1, and muscarinic receptors
Starting dose	3mg to 6mg every 12 hours[17]
Time to maximal effect	8 hours (4 hours with regular dosing)
Formulation	3 mg orodispersible tablets (Buccastem)
Indication	Dizziness, nausea
Common adverse effects	'Agitation; amenorrhoea; arrhythmias; constipation; dizziness; drowsiness; dry mouth; erectile dysfunction; galactorrhoea; gynaecomastia; hyperprolactinaemia; hypotension (dose-related); insomnia; leucopenia; movement disorders; neutropenia; parkinsonism; QT interval prolongation; rash; seizure; tremor; urinary retention; vomiting; weight increased'[16]
Contraindications	'Central nervous system depression; comatose states; phaeochromocytoma"[16]
Caution	Photosensitivity
Licencing	Licensed formulation
Benefits	Buccal alternative anti-emetic, widely used in clinical practice
Risks	Oral and skin reactions possible, constipating
Cost	£27.61 for 50×3 mg buccal tablets

Table 28 Risperidone orodispersible

Risperidone orodispersible	
What is it?	Anti-psychotic
Mechanism of action	'Risperidone is a dopamine D2, 5-HT2A, alpha1-adrenoceptor, and histamine-1 receptor antagonist' (British National Formulary).
Starting dose	0.5 mg OD (can be increased to BD if needed)
Time to effect	Hours to days
Formulation	Orodispersible tablet
Indication	Delirium, terminal agitation
Common adverse effects	'Anaemia; anxiety; appetite abnormal; asthenia; chest discomfort; conjunctivitis; cough; depression; diarrhoea; dyspnoea; epistaxis; fall; fever; gastrointestinal discomfort; headache; hyperglycaemia; hypertension; increased risk of infection; joint disorders; laryngeal pain; muscle spasms; nasal congestion; nausea; oedema; oral disorders; pain; sexual dysfunction; skin reactions; sleep disorders; urinary disorders; vision disorders; weight decreased'[16]
Contraindications	Hypersensitivity to the active substance or to any of the excipients
Caution	'Avoid in Acute porphyrias; cataract surgery (risk of intra-operative floppy iris syndrome); dehydration; dementia with Lewy bodies; prolactin-dependent tumours'[16] Seizure, Parkinsonism, renal and liver failure, old age[16]
Licencing	'Off label' use of a licensed formulation
Benefits	Orodispersible alternative anti-psychotic
Risks	Narrower spectrum of action than olanzapine, currently not widely use outside of psychiatry
Cost	£18.28 for 28×500 µg orodispersible tablets

Unlicensed alternatives that have been reported in the literature but are not listed in the BNF, PCF or APPM are not included. Consequently, the list of transmucosal drugs in this article may not include all those which some specialists may elect to use.

CONCLUSION

Transmucosal medications offer the possibility of enabling rapidly delivered needle-free symptom relief in the community without the need to wait for a healthcare practitioner to visit. However, the evidence base for their use via these routes is, largely, yet to be established.

A practical list of 27 medications has been identified and collated for healthcare professionals delivering care at the end of life to consider using in their practice. The list draws on existing knowledge of transmucosal delivery, in large part gained from clinical experience by colleagues in paediatric palliative care.

Should it be necessary to use this list of transmucosal drugs to deliver symptom management, then any experience gained should be combined and reported either on www.palliativedrugs.com or in the format of published articles. Combined with further research, this experience offers the possibility of reducing injection frequency and inherent delays in medication administration, particularly in the community setting.

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Contributors AES drafted the manuscript, undertaking the literature search and constructing the tables for each drug listed assisted by MP and EH. AES, MP, EH, MC, MM and ICKW jointly agree the drugs to include in the manuscript. MP, EH, MC, MM and ICKW had supervising input throughout the drafting the final manuscript.

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