Clinical Assessment and Management of Delirium in the Palliative Care Setting: Appendix

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Appendix: Medications* used for the management of delirium symptoms in palliative care [derived from references 1-3, and other references as indicated in the text]

While every effort has been made to ensure the accuracy of this text and medication doses, please also consult a pharmacist/pharmacy references and the manufacturer's Summary of Product Characteristic when prescribing these medications.

* No medication is currently licenced for use in the management of delirium. The use of medications for delirium management is therefore 'off-label'.

Note: There is currently very little literature detailing antipsychotic dose equivalency. There remains limited information from rigorous prospective randomized drug-drug comparison studies.

Some authors have suggested using a 2:1 ratio for PO: parenteral dosing for antipsychotics but, in clinical practice, clinicians tend to use a 1:1 ratio.

Abbreviations:

PO = by mouth

Subcut. = subcutaneous

IM = intramuscular

PR = per rectum

IV = intravenous

CSCI = continuous subcutaneous infusion

CIVI = continuous intravenous infusion

IR = immediate release

p.r.n. = pro re nata (when required)

CYP = cytochrome P450

EPS = extrapyramidal side effects

AP = antipsychotic

BDZ = benzodiazepine

EOL = end of life

"First-Generation" Antipsychotics (Formerly called "Typical"):

Haloperidol	Pharmacology	A butyrophenone antipsychotic Dopamine D_2 antagonist Onset of action: 10-15 mins Subcut.; >1 hour PO Time to peak plasma concentration: 2-6 hours (PO); 10-20 mins (Subcut.) Plasma half-life: 13-35 hours Average bioavailability of oral haloperidol is 60% -70% [4] However, in clinical practice most clinicians tend to use a 1:1 ratio for PO: Subcutaneous dosing Substrate of CYP1A2, CYP2D6, CYP3A4
	Advantages	Can be administered PO, Subcut., IM, and IV. (Note: ECG monitoring is recommended with IV haloperidol) Antiemetic properties
	Starting dose	Haloperidol 0.5-1mg PO (if patient willing to cooperate for oral dose) or Subcut. stat Add p.r.n. dose: e.g. 0.5 or 1mg PO/Subcut. q1h p.r.n. If scheduled dosing required: haloperidol 0.5-1mg PO/Subcut. 2 to 3 times daily • In elderly or frail patient, start with lower doses, e.g. 0.25-0.5mg, and titrate gradually
	Usual effective dose	Usual maximum: <5mg/24h Past prospective studies reported dose ranges of 0.25 - 10mg/day [5]
	Adverse effects	Extrapyramidal side effects (EPS) can occur, especially at higher doses: • Incidence is increased in slow metabolizers of CYP2D6 substrate, and reduced with parenteral administration May prolong QTc interval
	Other comments	• IV administration requires ECG monitoring [6] • Increased risk of *torsade des pointes,* ventricular fibrillation and sudden cardiac death if QTc interval >500msec or an increase of ≥60msec from baseline • Avoid using in patients with Parkinson's disease or dementia with Lewy bodies because of the risk of EPS

Levomepromazine (known as methotrimeprazine in some countries)	Pharmacology	A phenothiazine antipsychotic Dopamine D_2 antagonist Also H_1, ACh, α_1 adrenoreceptor, 5-HT_2 antagonist Onset of action: 30 mins Time to peak plasma concentration: 2-3 hours (PO); 30-90 mins (Subcut.) Plasma half-life: 15-30 hours Average bioavailability of oral levomepromazine is approx. 40% Substrate of CYP 3A4 (minor)
	Advantages	Sedating - may be advantageous in agitated patients Also antiemetic (use in lower doses for just antiemetic effect) Some analgesic effect Can be administered PO, Subcut. or deep IM
	Starting dose	Levomepromazine 5-12.5mg PO or Subcut. stat Add p.r.n. dose: e.g. 5-12.5mg PO/Subcut. q2h p.r.n. If scheduled dosing required: levomepromazine 10-25mg/ 24h in divided doses (2 to 3 times daily) • In elderly or frail patient, consider lower starting dose, e.g. 2.5mg • Higher starting dose may be required in very agitated palliative care patient
	Usual effective dose	50-100mg/24hrs Higher doses (up to 200mg/24h) may be required at the very end of life
	Adverse effects	Postural hypotension, paradoxical agitation, extrapyramidal side effects, anticholinergic effects
	Other comments	Note: Much longer time to peak concentration for Subcut. route compared with haloperidol Can cause inflammatory skin reaction at subcutaneous injection site: consider diluting with 0.9% saline if this occurs

<u>Chlorpromazine</u>	Pharmacology	A phenothiazine antipsychotic – *same class as Levomepromazine (methotrimeprazine)* Onset of action: 15 mins (IM – short-acting injection); 30-60mins (PO) Oral bioavailability: around 32% Substrate of CYP2D6 (major), CYP1A2 (minor), CYP3A4 (minor); inhibits CYP2E1 (weak)
	Advantages	Sedating Can be administered PO, PR, deep IM and IV (Availability of product formulations is country-dependent) (For deep IM and direct IV injections, administer *slowly*) (For direct IV injection, *dilute* solution with normal saline; can also administer as slow IV infusion) Rapid control of agitation (onset 15 mins) with IV route [7]
	Starting dose	Chlorpromazine 12.5-25mg PO or PR stat [8] Then, 12.5-50mg every 4 to 6 hours [9] In the elderly, use doses in the lower range of recommended adult dosing Use with caution in patients with renal and hepatic impairment
	Usual effective dose	50-150mg/24hrs [10] (In the elderly, use doses in the lower range of recommended adult dosing)
	Adverse effects	Postural hypotension, sedation, extrapyramidal side effects, anticholinergic effects May prolong QTc interval May increase the risk for falls due to orthostatic hypotension and somnolence
	Other comments	Chlorpromazine may cause local irritation with parenteral use [8]

"Second-Generation" Antipsychotics (Formerly called "Atypical"):

Olanzapine	Pharmacology	5-HT_{2A} and dopamine D_2 antagonist Onset of action: hours-days in delirium Time to peak plasma concentration: 5-8 hours Plasma half-life: 34 hours (52 hours in elderly) Average bioavailability of oral olanzapine is approx. 60% Substrate of CYP1A2 (major), CYP2D6 (minor); Inhibits DYP1A2 (weak), CYP2C19 (weak), CYP2C9 (weak)
	Advantages	Sedating (Therefore avoid using in patients with hypoactive delirium) Can be administered PO, IM or Subcut. [11] Available as oral disintegrating tablet (ODT) Antiemetic and anxiolytic properties [12]
	Starting dose	Olanzapine 2.5-5mg PO or Subcut. daily (usually at bedtime) *(Caution combining with benzodiazepine as risk of oversedation and respiratory depression)* Reduce dose in elderly and patients with hepatic impairment
	Usual effective dose	2.5-5mg PO/Subcut. at bedtime; may need to increase to 10mg at bedtime (Maximum daily dose is 20mg orally)
	Adverse effects	Drowsiness Orthostatic hypotension Metabolic effects (long term use)
	Other comments	The parenteral preparation of olanzapine has been administered subcutaneously with no injection site toxicity observed [11]
		From Breitbart's open-label study, patients with a poorer response to olanzapine were >70 years old (most predictive), had a history of dementia, CNS spread of cancer, hypoxia (as delirium etiology), delirium of 'severe' intensity (classified as Memorial Delirium Assessment Scale (MDAS) score >23) or hypoactive delirium. [13]

Quetiapine	Pharmacology	5-HT_{2A} and weak dopamine D_2 antagonist Onset of action (IR): hours in delirium Time to peak plasma concentration *(for immediate-release (IR) tablet format)*: 1.5 hours Plasma half-life (IR): 6 hours (10-14 hours in elderly) Substrate of CYP2D6 (minor), CYP3A4 (major)
	Advantages	Sedating Less likely to cause EPS than other atypical AP Antidepressant effect (low doses) [10]
	Starting dose *(Immediate release tablet format)*	Quetiapine (IR) 25mg PO 2 times daily If necessary, increase dose in 25-50mg increments Reduce dose in elderly and patients with hepatic impairment [14]
	Usual effective dose	40-100mg/24h
	Adverse effects	Drowsiness, dizziness Postural hypotension
	Other comments	Oral route only
		In patients with sleep-wake disturbance, sedating effects may be beneficial

Risperidone	Pharmacology	5-HT_{2A} and dopamine D_2 antagonist Onset of action: hours-days in delirium Time to peak plasma concentration: 1-2 hours Plasma half-life: 24 hours (clearance reduced by renal impairment) Substrate of CYP2D6 (major), CYP3A4 (minor), P-glycoprotein
	Advantages	Available as oral disintegrating tablet (ODT)
	Starting dose	Risperidone 0.5mg PO 2 times daily If necessary, increase dose by 0.5mg 2 times daily every 2^{nd} day Reduce dose in elderly and patients with severe renal or hepatic impairment [14] (Elderly without dementia: Max dose = 2mg/day CrCl <30ml/min: Max dose = 1.5mg/day Severe hepatic dysfunction: Max dose = 1mg/day)
	Usual effective dose	Usual maintenance dose: 1mg/24h Uncommon to use >3mg/24h (Increased risk EPS if dose >6mg/24h)
	Adverse effects	Insomnia, agitation, anxiety, drowsiness Postural hypotension
	Other comments	Oral route only
		In Kim's randomized, single-blind clinical trial, the response to risperidone was significantly poorer in patients ≥ 70 years old [15]

"Third-Generation" Antipsychotic:

Aripiprazole	Pharmacology	Has a unique pharmacological profile [16] A quinolinone antipsychotic Dopamine D_2 partial agonist, 5-HT_{1A} partial agonist, and 5-HT_{2A} antagonist Onset of action: 1 to 3 weeks Time to peak plasma concentration: oral 3-5 hours, IM immediate release: 1-3 hours Half-life: 75 hours (up to 146 hours in poor metabolizers of 2D6) Steady state reached: within 14 days of dosing. Average oral bioavailability is 87% (tablet), higher for oral solution [16] Substrate of CYP2D6 (major); CYP3A4 (major)
	Advantages	Can be administered PO or IM Available as oral disintegrating tablet (ODT), and oral solution Less EPS
	Starting dose	Aripiprazole 5mg PO or IM (immediate-release) daily Reduce dose in elderly: oral 2-5mg daily; IM immediate-release: initial 2.5mg to 10mg once; a repeat dose of 2.5 – 5mg may be given at 2 hours or greater intervals, NOT to exceed 15mg/day Reduce dose by 50% in poor metabolizers of CYP2D6
	Usual effective dose	5-20mg PO/IM daily (Maximum oral dose is 30mg once daily) For Geriatric – dementia psychosis (off-label use): max oral dose is 15mg per day
	Adverse effects	Headache 27%; Agitation (oral 19%, injection <1%); Anxiety, insomnia, nervousness, dizziness, sedation
	Other comments	Negligible effect on QTc interval in healthy patients [17] Little effect: prolactin levels, serum glucose and lipids [18]
		Partial agonism at D2 receptor may lead to improvement in attention, concentration, and sleep-wake cycle reversal in delirium [18]
		Systemic clearance strongly reduced by SSRI antidepressants paroxetine and fluvoxamine [16] *CYP2D6 and CYP3A4 drug-drug interactions, consult pharmacist/ pharmacy references for further details*
		In an open-trial of oral aripiprazole in 21 hospitalized cancer patients, delirium resolution rate after 7 days was higher in patients with hypoactive delirium, than the hyperactive patient cohort. Patients in the hyperactive cohort were older and had more frequent cognitive deficits, such as dementia [19]

Benzodiazepines (BDZs): **Note:** Specific BDZ antagonist = Flumazenil.

Midazolam	Pharmacology	Short-acting benzodiazepine (BDZ) Water soluble GABAmimetic (Affinity of midazolam for GABA receptor is 5-6 times greater than that of lorazepam) Onset of action: 5-10 mins Subcut; 2-3mins IV Plasma half-life: 1-4 hours Duration of action: 5mg <4hours, but interindividual variation Renal impairment: CrCL <10ml/min: Decrease dose by 50% Hepatic impairment: Caution Substrate of CYP2B6 (minor), CYP3A4 (major); Inhibits CYP2C8 (weak), CYP2C9 (weak)
	Advantages	Can be administered Subcut. or IV (may also be given IM) Rapid onset with rapid anxiolytic action Dose-dependent sedative effect Anticonvulsant BDZs are treatment of choice as monotherapy for alcohol or BDZ withdrawal
	Starting dose	Midazolam 2.5mg Subcut. q1h p.r.n., up to 5mg maximum Reduce dose in elderly/frail and in patients with non-malignant COPD e.g. 0.5-1mg Subcut. q1h p.r.n. If repeated doses needed for refractory agitated delirium at the end of life, consider 'palliative sedation' and continuous Midazolam CADD infusion: Usual initial rate 0.5-1mg/h CSCI or CIVI
	Usual effective dose	1-6mg/h CSCI or CIVI (BDZ tolerant patients may require higher doses) In extremely agitated patients, bolus/p.r.n. dose may need to be increased to 2.5-5mg q30-60mins p.r.n.
	Adverse effects	Dose dependent sedation, dizziness, incoordination Increased risk of falls Cognitive effects: deliriogenic, can cause amnesia Possible paradoxical reactions [20], with increased agitation, anxiety, insomnia
	Other comments	Use lower doses in frail or elderly patients Short half-life Titrate according to clinical response
		Cautions: (unless using in imminently dying patient) severe pulmonary insufficiency, severe liver disease, myasthenia gravis
		Caution: concurrent use with high dose olanzapine (Fatalities from oversedation or cardiorespiratory depression have been reported)

Lorazepam	Pharmacology	Intermediate-acting BDZ, half-life 12-24 hrs GABAmimetic. Peak effect approx. 30mins after IV administration [21], approx. 2hrs after PO or IM administration Plasma half-life: 10-20 hours In end stage renal disease, half-life elimination is approx. 18 hrs. Substrate: unknown
	Advantages	Can be administered PO, Sublingual, Subcut. or IV Rapid onset (N.B. If dry mouth, moisten mucous membranes before sublingual/buccal administration) Anticonvulsant BDZs are treatment of choice as monotherapy for alcohol or BDZ withdrawal
	Starting dose	Lorazepam 1mg Subcut. stat (up to 2mg maximum) - Use lower dose (e.g. 0.5mg) if co-administration with antipsychotic Reduce dose in elderly/frail and in patients with non-malignant COPD e.g. 0.25-0.5mg Subcut. stat For rapid tranquillisation of agitated patient, may need to be administered every 60mins ***Note: Lorazepam 1mg equivalent to Midazolam 2mg*** [22] If repeated doses needed for refractory agitated delirium at the end of life, consider 'palliative sedation': Lorazepam intermittent bolus: 0.05mg/kg every 2-4 hrs [21]
	Usual effective dose	1-2mg Subcut. q6-8h
	Adverse effects	Increased risk of falls Cognitive effects: deliriogenic, can cause amnesia Possible paradoxical agitation
	Other comments	Subcut. injection may be irritating to tissues as it is in a propylene glycol diluent Injectable drug should be refrigerated
		Less versatile for rapid titration than midazolam due to slower pharmacokinetics
		Use lower doses in frail or elderly patients
		Cautions: (unless using in imminently dying patient) severe pulmonary insufficiency, severe liver disease, myasthenia gravis
		Caution: concurrent use with high dose olanzapine (fatalities from oversedation or cardiorespiratory depression have been reported)

Other classes of medications:

Phenobarbital Phenobarbitone	Pharmacology	Barbiturate GABAmimetic A strong inducer of CYP3A and glucuronidation, thus reducing plasma concentrations of many drugs Onset of action after Subcut. administration 20-30 mins Plasma half-life: 2-6 days
	Advantages	Used in patients requiring 'palliative sedation' for refractory agitated delirium at the EOL Rapid onset ***(Note: Need for loading dose)*** May be useful in patients who have marked tolerance to benzodiazepines Anticonvulsant
	Starting dose if refractory agitated delirium not responding to BDZ:	Loading dose of Phenobarbital 60-120mg, by Subcut. or IM route, followed by 60mg 2 to 3 times daily From clinical experience, higher initial loading dose (e.g. 120mg) and higher scheduled Phenobarbital doses may be needed if delirious patient remains agitated despite optimisation of a Midazolam CADD infusion Dose should be titrated to desired effect or level of sedation Phenobarbital may also be given as a CSCI or CIVI infusion
	Usual effective dose	200 to 1200mg/24 hours Doses up to 3,800mg/24hrs have been reported
	Adverse effects	Paradoxical excitement in the elderly, agranulocytosis, thrombocytopenia, allergic skin reactions <3%, Stevens-Johnson syndrome (very rare)
	Other comments	Undiluted injection can be irritant as it is formulated in a mixture with propylene glycol IM injection can be given undiluted, otherwise dilute with WFI (water for injection) for Subcut. injection May also be given as slow diluted IV bolus, given over 2 mins ***Note: Phenobarbital should never be mixed with another drug due to incompatibilities***
		Also used: • In management of status epilepticus • As an alternative anticonvulsant in patients who are no longer able to take their usual PO maintenance anticonvulsant

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