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 D₂ 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 |

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BUSH SH, TIERNEY S, LAWLOR PG. August 2017
| Levomepromazine  
(known as methotrimeprazine in some countries) | Pharmacology | A phenothiazine antipsychotic  
Dopamine D$_2$ antagonist  
Also H$_3$, 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 |
| **Chlorpromazine** | 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<sub>2A</sub> and weak dopamine D<sub>2</sub> 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** | In patients with sleep-wake disturbance, sedating effects may be beneficial |

| **Risperidone** | **Pharmacology** | 5-HT<sub>2A</sub> and dopamine D<sub>2</sub> 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 |
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<tr>
<td><strong>Advantages</strong></td>
<td>Available as oral disintegrating tablet (ODT)</td>
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</table>
| **Starting dose** | Risperidone 0.5mg PO 2 times daily  
If necessary, increase dose by 0.5mg 2 times daily every 2<sup>nd</sup> 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 |
| **Other comments** | 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 $D_2$ 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.

<table>
<thead>
<tr>
<th><strong>Midazolam</strong></th>
<th><strong>Pharmacology</strong></th>
<th><strong>Specific BDZ antagonist</strong> = Flumazenil.</th>
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<tbody>
<tr>
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<td>Short-acting benzodiazepine (BDZ)</td>
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<td></td>
<td>Water soluble</td>
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<td></td>
<td>GABA mimetic</td>
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<td></td>
<td>(Affinity of midazolam for GABA receptor is 5-6 times greater than that of lorazepam)</td>
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<td></td>
<td>Onset of action: 5-10 mins Subcut; 2-3 mins IV</td>
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<td>Plasma half-life: 1-4 hours</td>
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<td>Duration of action: 5 mg &lt; 4 hours, but interindividual variation</td>
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<td>Renal impairment: CrCL &lt; 10 ml/min: Decrease dose by 50%</td>
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<td>Hepatic impairment: Caution</td>
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<td></td>
<td>Substrate of CYP2B6 (minor), CYP3A4 (major); Inhibits CYP2C8 (weak), CYP2C9 (weak)</td>
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<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Starting dose</strong></th>
<th><strong>Usual effective dose</strong></th>
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<tbody>
<tr>
<td>Can be administered Subcut. or IV (may also be given IM)</td>
<td>Midazolam 2.5 mg Subcut. q1h p.r.n., up to 5 mg maximum</td>
<td>1-6 mg/h CSCI or CIVI (BDZ tolerant patients may require higher doses)</td>
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<tr>
<td>Rapid onset with rapid anxiolytic action</td>
<td>Reduce dose in elderly/frail and in patients with non-malignant COPD e.g. 0.5-1 mg Subcut. q1h p.r.n.</td>
<td>In extremely agitated patients, bolus/p.r.n. dose may need to be increased to 2.5-5 mg q30-60 mins p.r.n.</td>
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<td>Dose-dependent sedative effect</td>
<td>If repeated doses needed for refractory agitated delirium at the end of life, consider ‘palliative sedation’ and continuous Midazolam CADD infusion: Usual initial rate 0.5-1 mg/h CSCI or CIVI</td>
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<tr>
<td>Anticonvulsant</td>
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<tr>
<td>BDZs are treatment of choice as monotherapy for alcohol or BDZ withdrawal</td>
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<tr>
<th><strong>Adverse effects</strong></th>
<th><strong>Other comments</strong></th>
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<tbody>
<tr>
<td>Dose-dependent sedation, dizziness, incoordination</td>
<td>Use lower doses in frail or elderly patients</td>
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<tr>
<td>Increased risk of falls</td>
<td>Short half-life</td>
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<tr>
<td>Cognitive effects: deliriogenic, can cause amnesia</td>
<td>Titrate according to clinical response</td>
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<tr>
<td>Possible paradoxical reactions [20], with increased agitation, anxiety, insomnia</td>
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**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)
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  | Pharmacology | Barbiturate  
| Phenobarbitone |             | 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  

Bush SH, Tierney S, Lawlor PG. August 2017
References:


