Non-Conventional Medication Formulations

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## Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Acute disturbance</strong></td>
<td>Composite term = agitation + violence</td>
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<tr>
<td><strong>De-escalation</strong></td>
<td>Process of helping someone achieve a calmer mental state (verbal + non-verbal approaches)</td>
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<tr>
<td><strong>Pro re nata (PRN) medication</strong></td>
<td>Voluntary use of medication for agitation (regardless of route)</td>
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<tr>
<td><strong>Rapid tranquillisation</strong></td>
<td>Use of medication by the parenteral route (IM/IV), when urgent sedation is necessary</td>
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Spectrum of acute disturbance

Pre-RT = pre-emptive use of de-escalation + PRN

Mild agitation

Moderate agitation

Severe agitation

RT & restrictive interventions
Why consider non-conventional formulations?

Pre-RT phase and advance care planning
- Increased patient choice
- Collaboration in care planning
- Prescribing NOT routine

Pharmacokinetic profiles
- Increased onset of action
- Improving adherence
Non-conventional formulations

- **Orally Disintegrating**
  - Olanzapine
  - Risperidone
  - Aripiprazole

- **Buccal**
  - Midazolam

- **Sublingual**
  - Asenapine
  - Lorazepam

- **Inhaled**
  - Loxapine
Primer on Pharmacokinetics

A: Intranasal & Oro-buccal
B: Inhaled
C: Oral

- **Absorption**
  - Uptake of substances across tissues

- **Bioavailability**
  - Degree/rate of absorption into living tissue
  - Amount of physiologically available drug

- **Distribution**
  - Proportion in different tissues

- **Metabolism**
  - Process of break-down of drug, sometimes into active substances
  - ‘First pass’

- **Excretion**
  - Elimination from the circulation (e.g. urine, bile, sweat)

\[ T_{max} = \text{time to peak plasma levels (proxy)} \]
Orally disintegrating antipsychotics

- Dissolve with saliva, no fluids needed
- May improve adherence
- Patients with swallowing difficulties
- Pharmacological properties equivalent same as oral antipsychotic
  - Absorbed through GI tract with 'first pass' metabolism

Aripiprazole
Olanzapine
Risperidone

Risperidone orally disintegrating tablets
ODAS: Evidence and guidelines

- Trial evidence (6 RCTs) supporting effectiveness for agitation in psychosis (Mullinax 2017)
- Similar effect sizes to IM first gen APs, similar SEs
- Recommended by BAP NAPICU guideline (2018)
- Included alongside conventional oral
Sublingual asenapine

• Second generation antipsychotic (dibenzo-oxepino pyrrole)

• Dissolves under tongue

• Standard route for asenapine due to very high first pass metabolism
  • Practical problem: ineffective if swallowed

• Side effects include: sedation, anxiety, nausea, oral hypoesthesia, extra-pyramidal side effects and akathisia (SPC)

\[ T_{\text{max}} = 30-90\text{mins} \]
Sublingual asenapine: Evidence and guidelines

- Systematic review (Citrome 2009)
  - Effective for acute SZ/BPAD

- One double-blind, placebo RCT, N = 120 (Pratts 2014)
  - Effect size comparable to IM AP, effect as early as 15 mins

- Maudsley Prescribing Guidelines (13th Ed)
  - Pratts 2014 discussed – not in summary recommendations
Buccal midazolam

- Water soluble benzodiazepine, commonly used in epilepsy
- Rapidly absorbed through buccal mucosa with high bioavailability
- Faster onset of action than oral/IM
- Side effects include: sedation, **respiratory depression**, nausea and vomiting (SPC)

$T_{max} = 15-90\text{mins}$
Buccal midazolam: Evidence and guidelines

TREC (2003) - IM Midazolam effective for agitation

Service evaluation on 2 PICUS, N = 27 (Taylor et al 2008) - Buccal midazolam reduced agitation within 30 mins in 70% participants + reduced IM injections

Recommended by BAP NAPICU guideline (2018) - Pre-RT phase of algorithm
Inhaled Loxapine

- First generation AP (dibenzoxapine tricyclic)
- Administered using a fast-heating inhalation device, requiring patient cooperation to breathe the active agent in
- Rapidly absorbed, higher bioavailability than oral
- Side effects include: extrapyramidal adverse effects akathisia, drowsiness, dry mouth, constipation and changes in weight (SPC)
- **NB:** Concern re bronchospasm – contraindicated in COPD/Asthma

$T_{max} = 2-3\text{mins}$
**Inhaled Loxapine: Evidence and guidelines**

**Phase II & III trials (Patel and Sethi 2018)**

- Rapid onset of action, improvement in PANNS-EC after 10mins Vs placebo


- Pre-RT phase of algorhythm
Sublingual lorazepam

• Paucity of evidence for lorazepam monotherapy but widely used (90% of oral medication, POMH-UK survey 2017)

• Dissolving under tongue significantly reduces Tmax – equivalent to intramuscular (Pzifer 2019)

• However - No licensed sublingual preparation currently exists

• S/L lorazepam is not mentioned in current guidelines

Tmax = 60 mins (versus 90 mins oral)
## Pharmacokinetic summary

<table>
<thead>
<tr>
<th>Medication</th>
<th>Time to peak plasma levels ($T_{\text{max}}$)</th>
<th>Bioavailability</th>
<th>Administration remarks</th>
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<tbody>
<tr>
<td>Oral lorazepam</td>
<td>2 hours</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Sublingual lorazepam</td>
<td>60 mins</td>
<td>100%</td>
<td>Tablets can be dissolved under the tongue.</td>
</tr>
<tr>
<td>Buccal midazolam</td>
<td>30 minutes</td>
<td>75%</td>
<td>Buccal has a significantly faster onset of action (as compared to standard oral treatment). Licensed for treatment of status epilepticus.</td>
</tr>
<tr>
<td>Orally disintegrating aripiprazole</td>
<td>3-5 hours</td>
<td>87%</td>
<td>Well absorbed from the gastrointestinal tract after oral doses.</td>
</tr>
<tr>
<td>Sublingual asenapine</td>
<td>30-90 minutes</td>
<td>35% (&lt;2% if ingested orally)</td>
<td>Eating and drinking should be avoided for 10 minutes after administration.</td>
</tr>
<tr>
<td>Inhaled loxapine</td>
<td>2 minutes</td>
<td>High</td>
<td>Contraindicated in patients with acute respiratory distress or with active airways disease.</td>
</tr>
<tr>
<td>Orally disintegrating olanzapine</td>
<td>5-8 hours</td>
<td>Undetermined</td>
<td>Well absorbed from the gastrointestinal tract after oral doses but undergoes considerable first-pass metabolism.</td>
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<tr>
<td>Orally disintegrating risperidone</td>
<td>1-2 hours</td>
<td>70%</td>
<td>Readily absorbed after oral doses.</td>
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<tr>
<td>Oral promethazine</td>
<td>2-3 hours</td>
<td>25%</td>
<td>Licensed for allergic conditions and insomnia.</td>
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What role for non conventional medication?

• Combination of high quality de-escalation techniques with rapidly acting non-conventional formulations may enhance the management of early agitation

• Now in some formularies but rarely used in practice

• More research needed!
Take Home Messages

- Increased patient choice + engagement
- Practical and pharmacokinetic advantages
- Prescribing should be tailored to individual’s needs
- More trials needed to optimize de-escalation/management of mild-moderate agitation
References


• Maudsley Prescribing Guidelines (13th Edition)