Non-Conventional Medication Formulations

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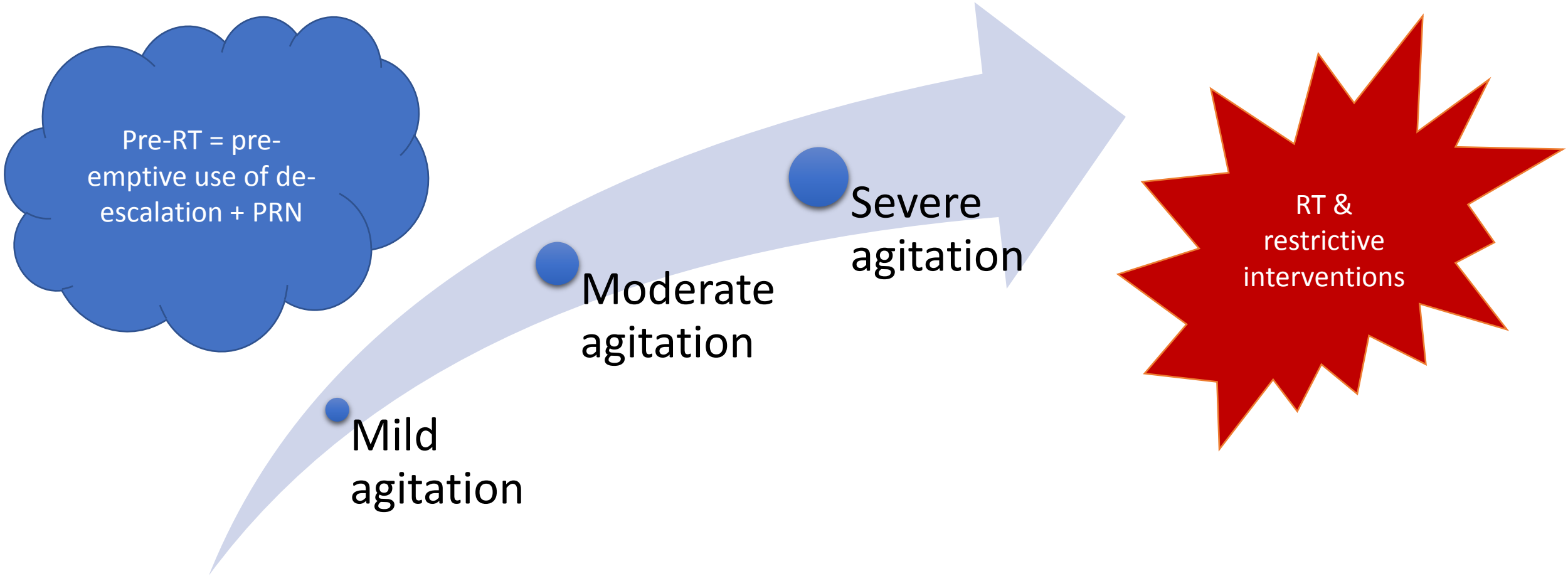
Outline

- Definitions
- Pharmacokinetics primer/refresher
- Non-conventional formulations
- Current guidance
- Looking ahead

Definitions

Acute disturbance	• Composite term = agitation + violence
De-escalation	• Process of helping someone achieve a calmer mental state (verbal + non-verbal approaches)
Pro re nata (PRN) medication	• Voluntary use of medication for agitation (regardless of route)
Rapid tranquilisation	• Use of medication by the parenteral route (IM/IV), when urgent sedation is necessary

Spectrum of acute disturbance



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

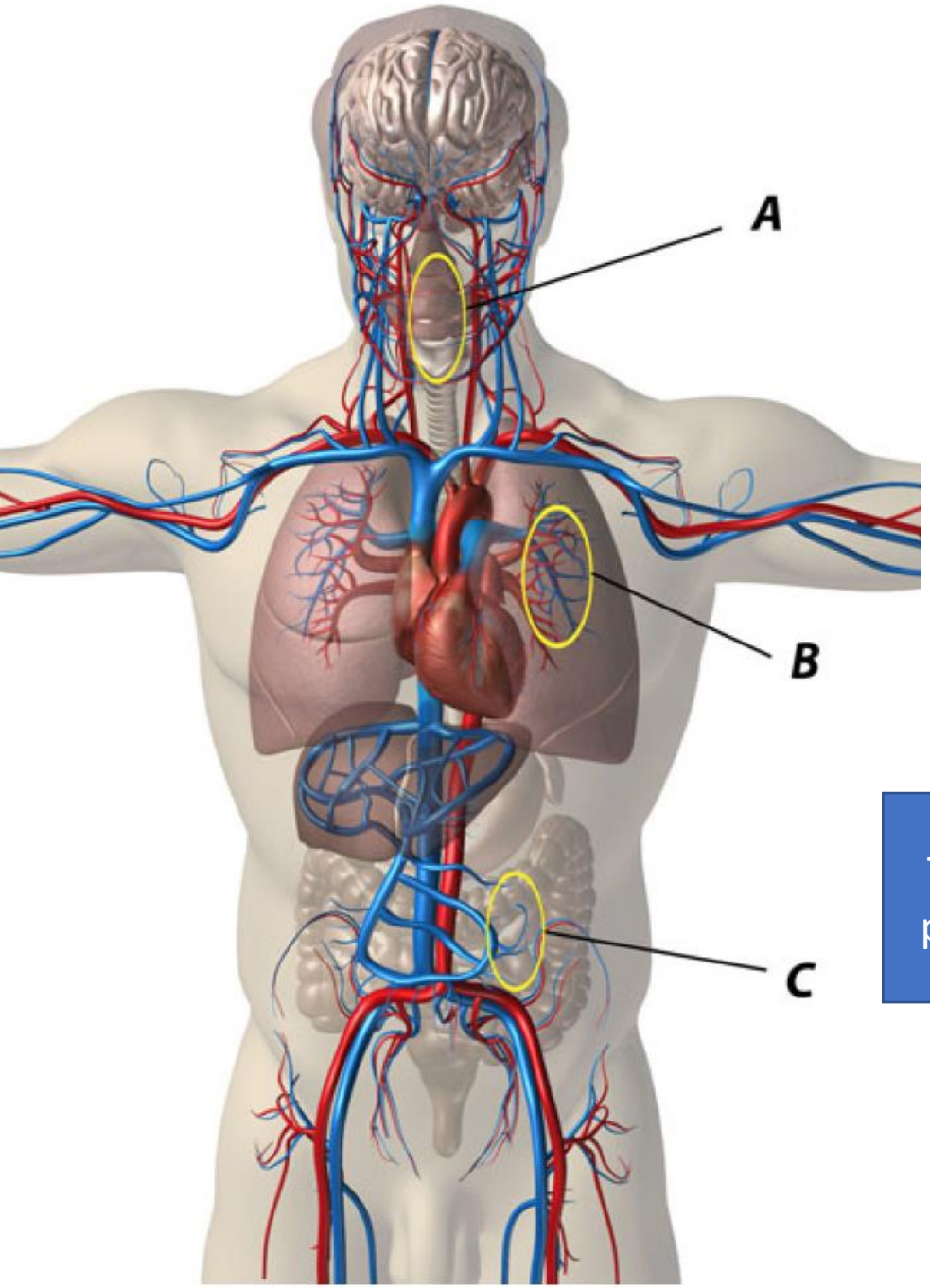
- Midazolam

Sublingual

- Asenapine
- Lorazepam

Inhaled

- Loxapine



Primer on Pharmacokinetics

A: Intranasal & Oro-buccal

B: Inhaled

C: Oral

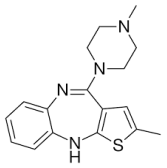
Tmax = time to peak plasma levels (proxy)

- **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)

Orally disintegrating antipsychotics

Aripiprazole

Olanzapine

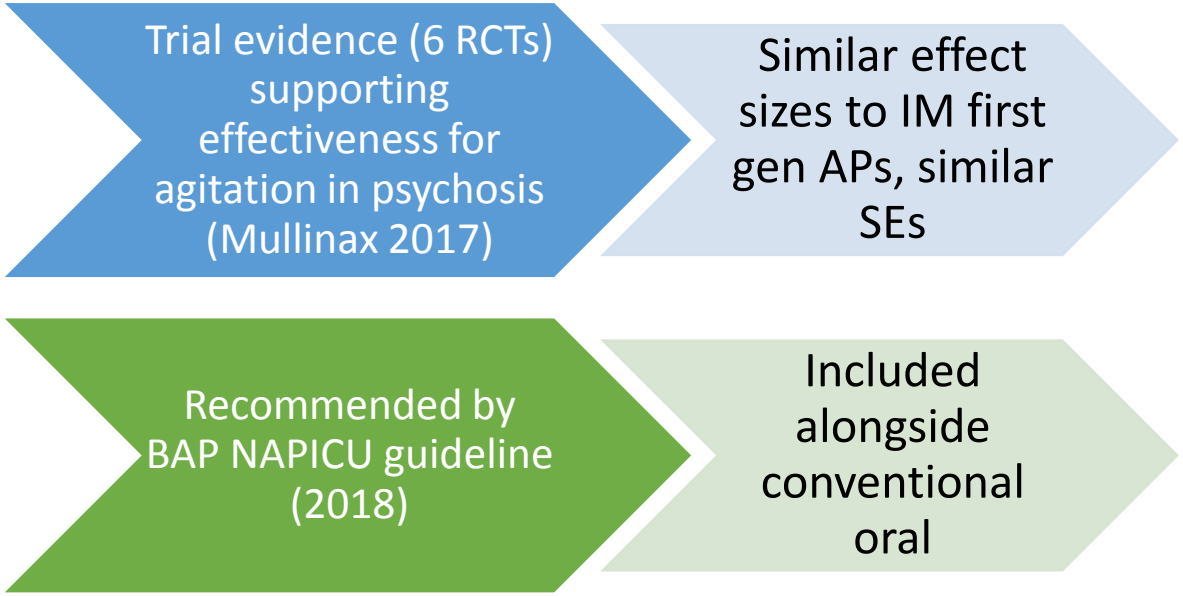


Risperidone

- 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*

Risperidone orally disintegrating tablets

ODAS: Evidence and guidelines

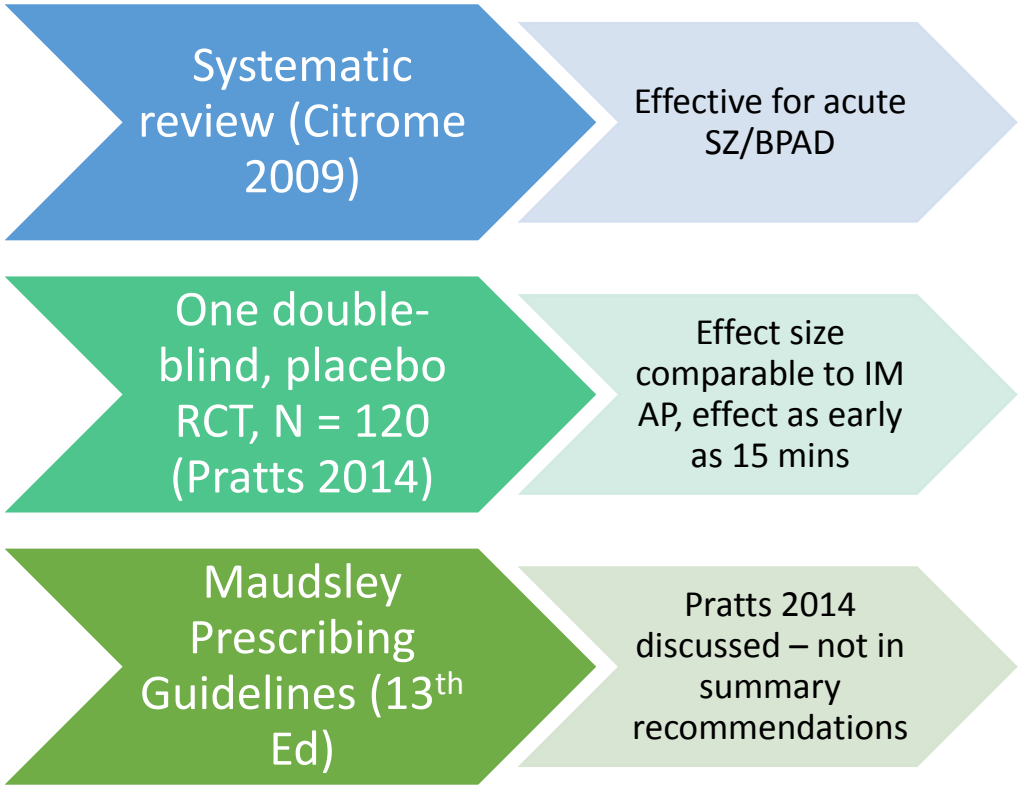


Sublingual asenapine

- 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 hypoaesthesis, extra-pyramidal side effects and akathisia (SPC)

Tmax = 30-90mins

Sublingual asenapine: Evidence and guidelines

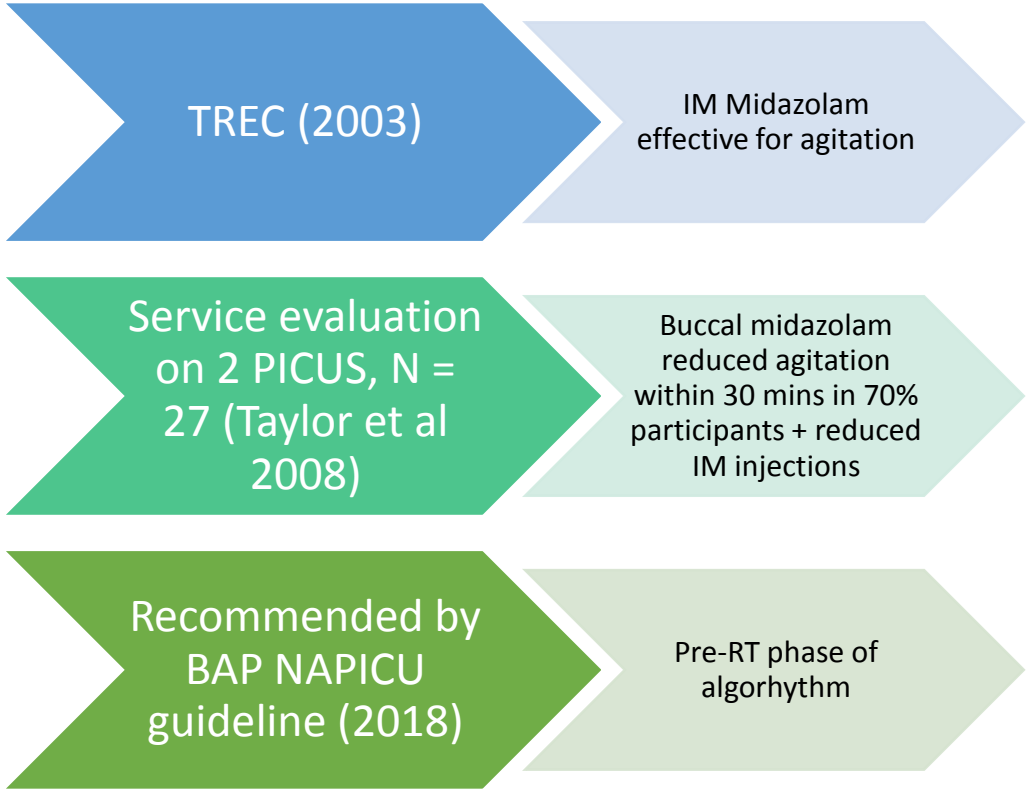


Buccal midazolam

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

Tmax = 15-90mins

Buccal midazolam: Evidence and guidelines



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

Tmax = 2-3mins

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

Recommended by BAP NAPICU guideline (2018)

AND Maudsley Prescribing Guidelines (13th Ed)

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

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

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

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- Pfizer (2019b) Canadian medication information on Ativan. Available: https://www.pfizermedicalinformation.ca/en-ca/ativan