Joint BAP NAPICU evidence based guidelines for the clinical management of acute disturbance (de-escalation and rapid tranquillisation)

Oral options

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Declaration of interests

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napicu
national association of psychiatric intensive care & low secure units

NHS
Central and North West London
NHS Foundation Trust

Practical challenges of oral “pre-RT”

- Concurrently with further de-escalation – not escalation
- Patient agreement and co-operation

Formulations

- Oral tablets, oro-dispersible tablets, liquids – GI absorption
  - Oro-dispersible tablets designed to dissolve on contact with saliva or water – but still require swallowing
- Buccal formulations (liquids) – buccal mucosal absorption
- Oral inhalations (powders) – respiratory absorption

Pharmacokinetic principles

- PK of different formulations of the same drug can vary markedly
  - time to peak plasma concentration (Tmax) is a crude gauge for time to onset of action (usually some level of sedation)
- Complex interplay between absorption, Tmax, time to onset of action, duration of effect, t½ and risk of acute side effects
- Oral formulations absorbed via the GIT have the longest Tmax
- Hepatic ‘first-pass’ - adjust parenteral doses accordingly
- Buccal, sublingual and oral-inhaled formulations have similar or shorter Tmax compared with IM

Pharmacokinetics

Table 3. Benzodiazepine formulations

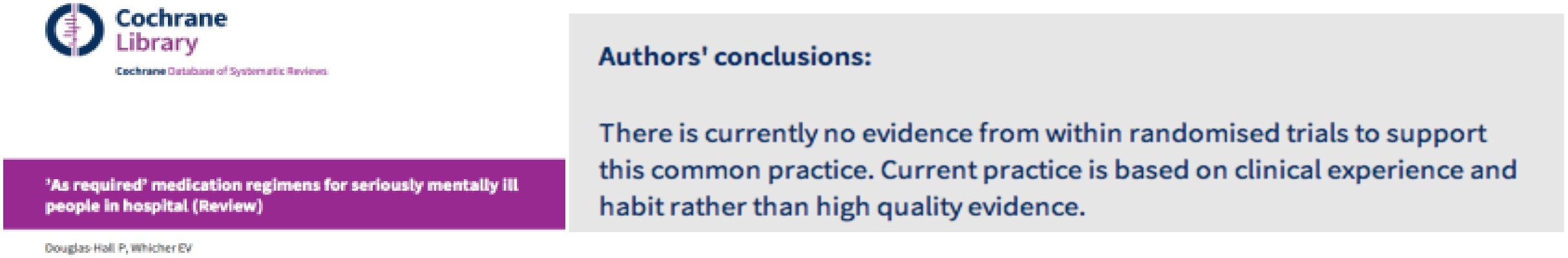
Medication	Route	Formulation	Bioavailability	Time to maximum plasma concentration (Tmax)
Clonazepam	Oral	Tablets	90%	1–4 hours
		Liquid	90%	1–4 hours
	IM	Injection	93%	3 hours
Diazepam	Oral	Tablets	76%	30–90 minutes
		Liquid	76%	30–90 minutes
	IM	Injection	Erratic	Erratic
	IV	Injection (emulsion)	100%	≤ 15 minutes
Lorazepam	Oral	Tablets	100%	2 hours
	IM	Injection	100%	1–1.5 hours
	IV	Injection	100%	seconds/minutes
Midazolam	Buccal	Oromucosal solution	75%	30 minutes
	IM	Injection	>90%	30 minutes
	IV	Injection	100%	seconds/minutes

Table 5. Antipsychotic formulations

Medication	Route	Formulation	Bioavailability	Time to maximum plasma concentration (Tmax)
Aripiprazole	Oral	Tablet	87%	3–5 hours
	Oral	Oro-dispersible	87%	3–5 hours
	Oral	Liquid	87%	3–5 hours
	IM	Injection	100%	1 hour
Droperidol	Oral	Tablet	75%	1–2 hours
	IM	Injection	100%	≤ 30 minutes
	IV	Injection	100%	seconds/minutes
Haloperidol	Oral	Tablet	60–70%	2–6 hours
	Oral	Liquid	60–70%	2–6 hours
	IM	Injection	100%	20–40 minutes
	IV	Injection	100%	seconds/minutes
Olanzapine	Oral	Tablet	Undetermined	5–8 hours
	Oral	Oro-dispersible	Undetermined	5–8 hours
	IM	Injection	Undetermined	15–45 minutes
	IV	Injection	100%	seconds/minutes
Quetiapine	Oral	Tablet	Unknown	1.5 hours
Risperidone	Oral	Tablet	67%	1–2 hours
	Oral	Oro-dispersible	67%	1–2 hours
	Oral	Liquid	70%	1–2 hours

Evidence of efficacy for “pre-RT”

- Data gap
  - Small trials, mixed routes of administration Oral+IM vs others, oral vs IM…..
- No RCTs comparing the efficacy of PRN medication with regular medication for the treatment of psychotic symptoms or acute disturbance



Douglas-Hall P, Whicher EV (2015) ‘As required’ medication regimens for seriously mentally ill people in hospital. *Cochrane Database Syst Rev* (12): CD003441.

Evidence of efficacy for oral benzodiazepines

Data is very sparse

- **Buccal midazolam: a** small service evaluation (n = 27), reduced agitation (Behavioural Activation Rating Scale) in 70% of participants within 30 minutes (Taylor et al. 2008)
- **Alprazolam:** randomised double-blind trial or oral alprazolam plus oral haloperidol versus oral haloperidol alone (n = 28) (Barbee et al. 1992)
- No studies evaluating oral **lorazepam**, **clonazepam** or **diazepam** monotherapy
- **Lorazepam**: larger trial (n = 162) compared oral risperidone+oral lorazepam vs IM haloperidol+IM lorazepam (Currier et al 2004) replicated earlier findings (n = 37; Foster et al., 1997)
  - Both oral and IM lorazepam had a similar clinical effect by 30 mins, effects of both lasting for at least 120 mins: no efficacy advantage of IM lorazepam over oral

Cochrane Library

Cochrane Database of Sys

1.1.2. No power

The trial search did not identify trials that compared specific benzodiazepines at a high versus low dose; oral versus IM/intravenous; or low frequency versus high frequency (as defined by each study). Future research could examine these comparisons to highlight any potential benefits/efficacy of specifically named benzodiazepines in the management of psychosis-induced aggression/agitation.

Benzodiazepines for psychosis-induced aggression or agitation (Review)

Zaman H, Sampson SJ, Beck ALS, Sharma T, Clay FJ, Spyridi S, Zhao S, Gillies D

Evidence of efficacy for oral antipsychotics (1)

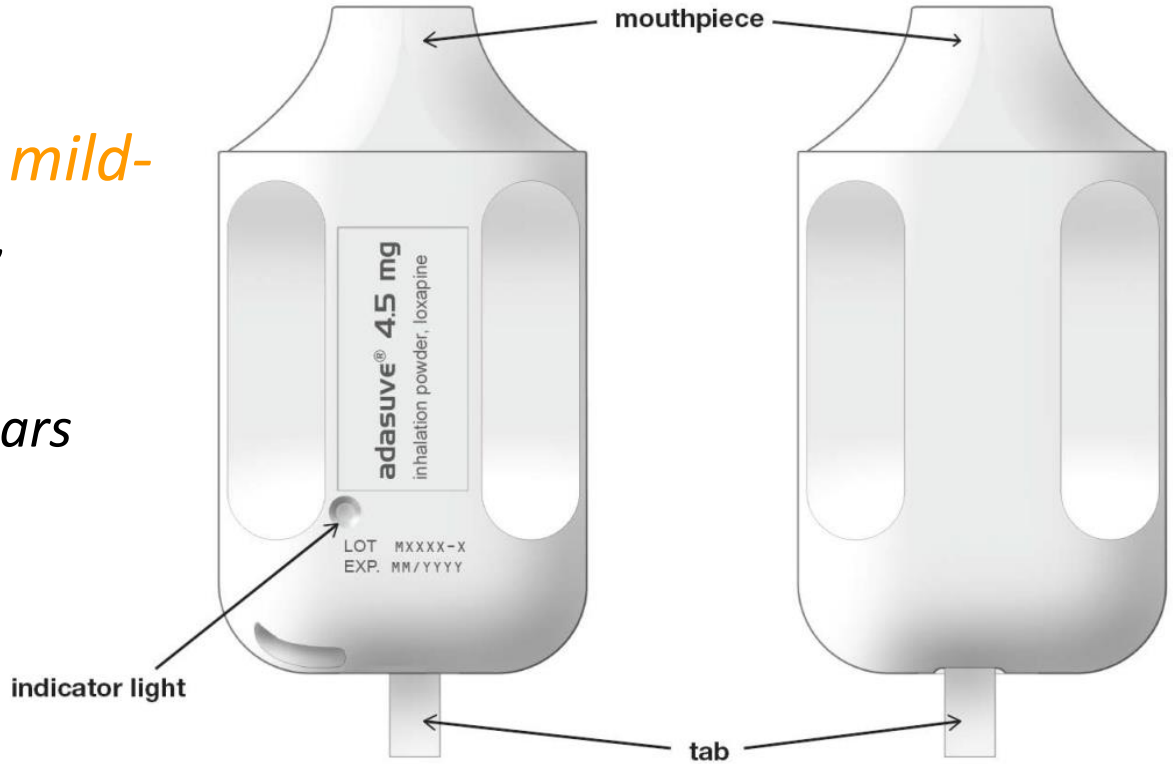
- **Olanzapine**:
  - Oro-dispersible olanzapine vs risperidone liquid (n = 87), equally effective in reducing PANSS-EC scores, no difference in need for additional injections (Hatta et al., 2008)
  - Oral olanzapine vs oral aripiprazole RCT 5-days (n = 604): significant improvements in PANSS-EC scores, no difference between groups, but greater proportion of aripiprazole patients also required lorazepam (Kinon et al., 2008).
  - Olanzapine oro-dispersible or IM olanzapine four arm RCT: significantly greater improvements in PANSS-EC scores compared to IM haloperidol (n = 42) (Hsu et al. 2010).
- **Risperidone:**
  - RCT (n = 162) single dose oral risperidone+oral lorazepam compared to IM haloperidol+IM lorazepam, mean PANSS-EC at 30, 60, and 120 mins were stat. sig. improved at each time point ($p<0.0001$) in both groups, no difference between the groups (Currier et al., 2004); these strategies are equally effective (Reviewed by Currier and Medori 2006)
  - Oral risperidone+oral lorazepam versus IM FGAs +/-IM lorazepam (n=226) and found oral risperidone+ oral lorazepam more successful at 2hrs plus less EPS than with IMs (Lejeune et al., 2004).
  - Oro-dispersible risperidone vs IM haloperidol: randomised open prospective study, PANSS-EC score significantly decreased in both groups, no significant difference (Lim et al., 2010).
  - Liquid 3mg, (n = 42) RCT 4 treatment arms: PANSS-EC and ACES improved over 24hrs (Hsu et al. 2010)

Evidence of efficacy for oral antipsychotics (2)

- **Quetiapine**
  - 5-day study (n = 36) suggested effectiveness, mean OAS scores reduced (Ganesan et al. 2005)
- **Haloperidol**
  - Trials in combination with IM lorazepam (Veser et al., 2006).
  - A prospective study (n = 101) over 72 hrs compared oral SGAs (risperidone, olanzapine and quetiapine) vs oral haloperidol: all effective, decreases in scores in BPRS and MOAS: no significant differences between groups. EPS were more common in the haloperidol group (21.4%) than risperidone (7.4%), olanzapine (0%) or quetiapine (0%) groups (Villari et al., 2008).
- Small studies explored relative effectiveness of oral vs IM antipsychotics: little difference
- Review (Mullinax et al. 2017) only six small studies (n = 464). Generally, oral SGAs were effective & had side-effects comparable to FGAs

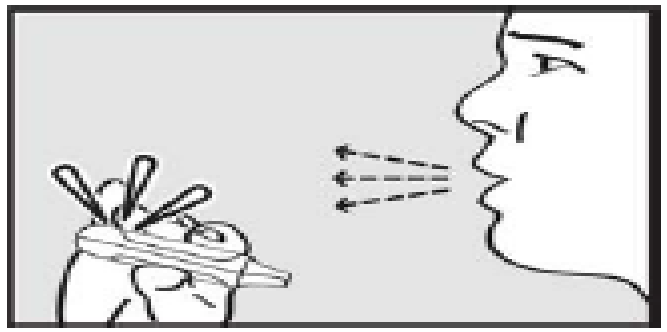
Loxapine Inhalation

- *Licensed in the UK for "the management of mild-to-moderate agitation in adults with schizophrenia or bipolar affective disorder."*
- *Typical antipsychotic*
  - *Used orally & IM in some countries for many years*
- *10mg inhaled Tmax:* ***1.13minutes*** *(median)*
  - *25%: 1 minute 75%: 2 minutes*
- $t_{1/2}$*: mean* 7.61 hours ± 1.87 SD
- Most common AEs:
  - Dysgeusia , throat irritation, few cases of EPS (dystonia, akathisia)
- Pulmonary AEs: Patients with clinically significant acute or chronic pulmonary diseases were excluded from phase II and III studies
- Contraindicated in patients with a history of or current diagnosis of asthma and COPD, or other lung diseases associated with bronchospasm, or lung diseases with acute respiratory symptoms
- No effects on the cardiovascular system

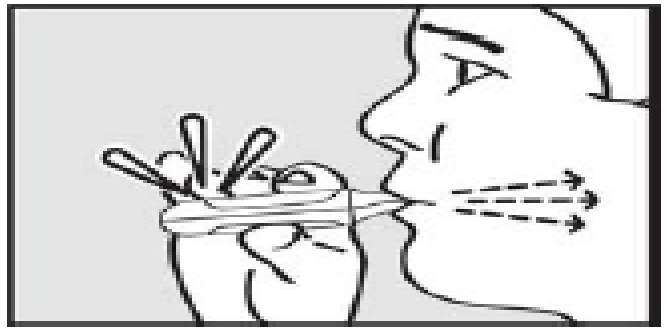


Must have on-site access to equipment to manage acute bronchospasm (i.e. Short-acting ß-agonist).

Instruct the patient to:

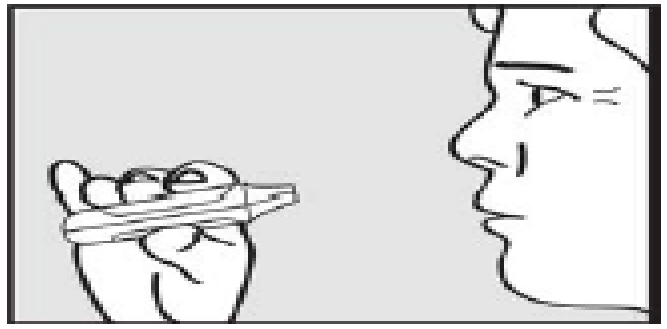


3. Exhale
Hold the inhaler away from the mouth and breathe out fully to empty lungs.



4. Inhale
Inhale through the mouthpiece with a steady deep breath.

IMPORTANT: Check that the green light turns off after the patient inhales.



5. Hold breath
Remove the mouthpiece from the mouth and hold breath briefly.

NOTE: If the green light stays on after the patient inhales, instruct the patient to repeat steps 3-5.

Evidence of efficacy for inhaled loxapine

Authors	Year	Study sample	Study design	N	Dosage (mg/d)	Main findings
Allen et al.	2011	Schizophrenia schizoaffective disorder	RCT, phase II	129	5 or 10mg Single dose	Rapid improvement, safe and well tolerated
Lesem et al.	2011	Schizophrenia	RCT, phase III	344	5 or 10mg Multiple doses	Effective and well tolerated
Kwentus et al.	2012	Bipolar I	RCT, phase III	314	5 or 10mg	Rapid, well tolerated

Allen MH, Feifel D, Lesem MD, et al. (2011) Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 72: 1313–1321.
Lesem MD, Tran-Johnson TK, Riesenberg RA, et al. (2011) Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. *Br J Psychiatry* 198: 51–8.
Kwentus J, Riesenberg RA, Marandi M, et al. (2012) Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipol Disord* 14: 31–40.

Evidence of efficacy for levomepromazine (methotrimeprazine)

- Available as oral tablets and solution for injection
- Tmax is 1–3 hours for the oral route (bioavailability 50–60%), and 30–90 minutes for the IM route.
- Common side-effects include QT prolongation and hypotension
- No published studies for efficacy of oral as monotherapy pre-RT
- A randomised open trial (n = 19), comparing oral haloperidol vs oral haloperidol+oral levomepromazine found no clear difference between groups

Higashima M, Takeda T, Nagasawa T, et al. (2004) Combined therapy with low potency neuroleptic levomepromazine as an adjunct to haloperidol for agitated patients with acute exacerbation of schizophrenia. *Eur Psychiatry* 19(6): 380–381.

Evidence of efficacy for promethazine

- Antihistamine, with sedative properties
- Its onset of sedative effect ranges from 20–30 minutes (oral and IM), Tmax is 2–3 hours (oral/IM)
- Effects last 4–6 hours but may persist for as long as 12 hours after oral administration

- No studies have evaluated the use of oral (or IM) monotherapy in RT

Current practice - recommendations

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Review Article

Current rapid tranquillisation documents in the UK: a review of the drugs recommended, their routes of administration and clinical parameters influencing their use

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[1]*Deputy Chief Pharmacist, East London NHS Foundation Trust, UK;* [2]*Consultant Psychiatrist, South London and Maudsley NHS Foundation Trust, UK*

RT guideline documents (2012), n=45

PO: **Lorazepam** and **haloperidol**
Olanzapine, risperidone

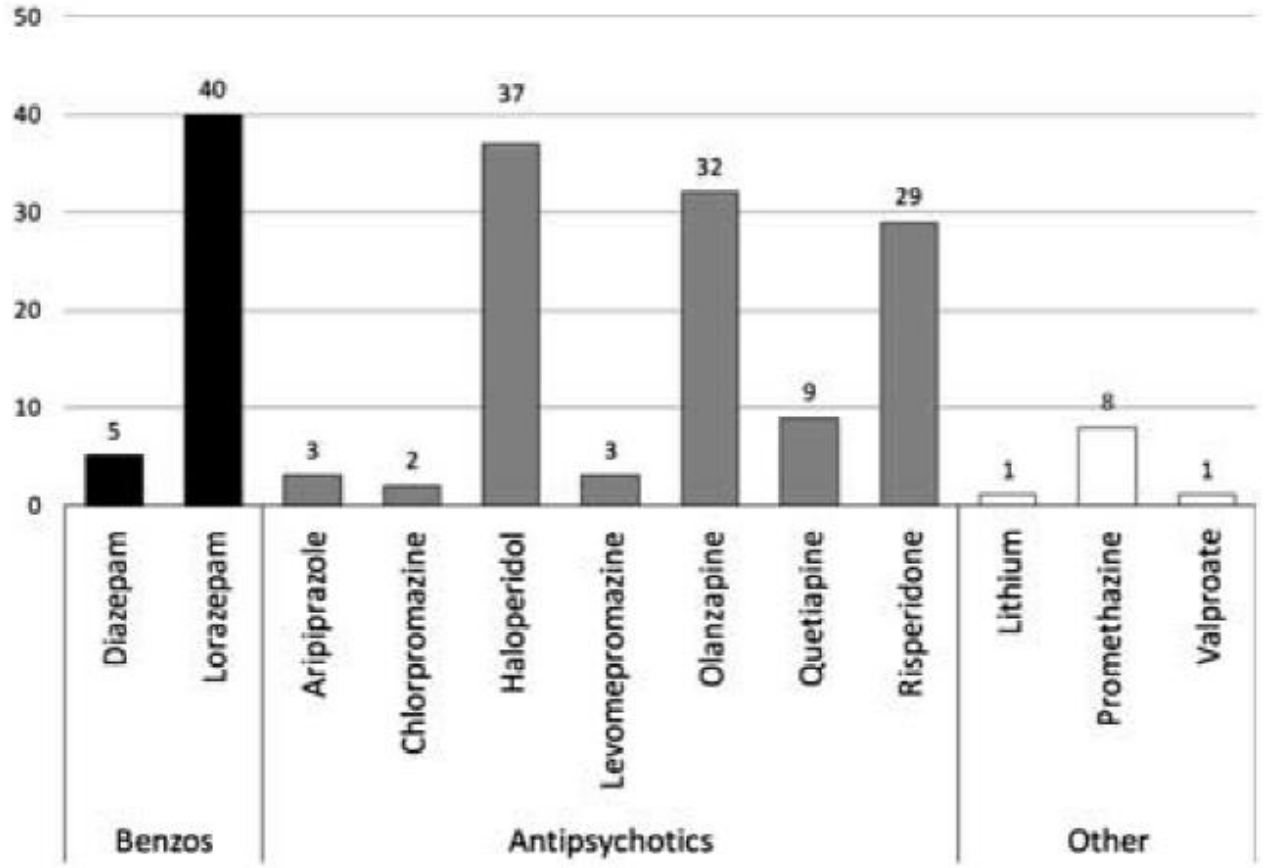
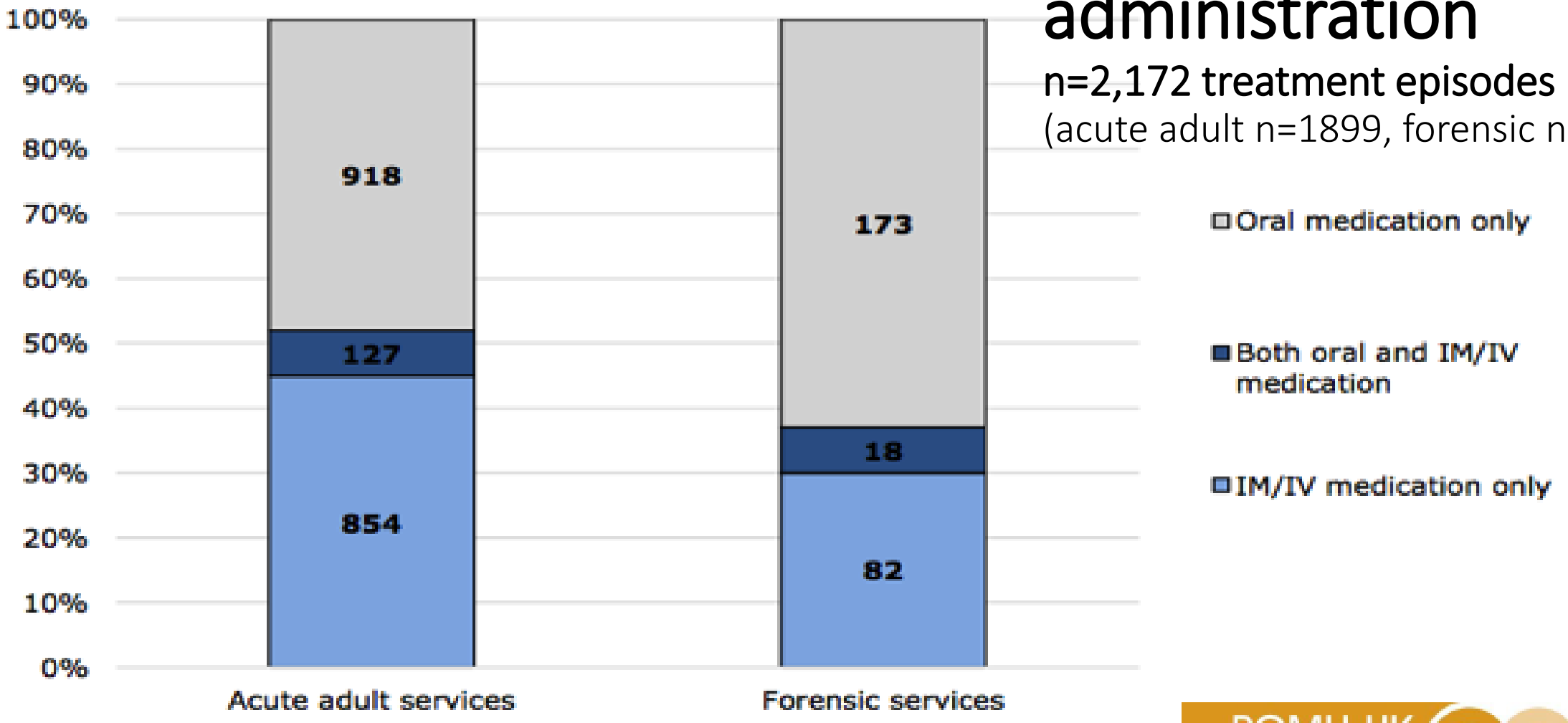


Figure 1. *Drugs recommended for oral use in RT*

Current practice – POMH data

Route of medicine administration

n=2,172 treatment episodes
(acute adult n=1899, forensic n=273)



Oral-only medication was given in half the episodes (n = 1091; **50**%)

Oral	Antipsychotic	Benzodiazepine	Promethazine
Antipsychotic*	12% (n=143)		
Benzodiazepine**	14% (n=169)	59% (n=726)	
Promethazine	2% (n=22)	5% (n=66)	7% (n=92)

* haloperidol (72%), quetiapine (10%), olanzapine (8%), risperidone (5%)
** lorazepam (91%)

N = 2,172 treatment episodes
N = 1,097 episodes of oral

The choice of oral benzodiazepine was **lorazepam** in over 90% of cases, median dose: 1mg

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Oral **promethazine**: was used in n=198 episodes (alone or combinations), median dose: 50mg

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Haloperidol was most commonly used oral antipsychotic: 72% of cases, median dose: 5mg
Oral **promethazine**: was used in n=198 episodes (alone or combinations), median dose: 50mg
81% (n = 1756) patients already prescribed regular antipsychotic(s)

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Oral antipsychotics administered (n=352)

Oral antipsychotic medication administered for the episode	n	% of all episodes in which oral antipsychotic medication was prescribed	Median dose (mg)	Dose range (mg)
Haloperidol	253	72%	5	0.5-25mg
Quetiapine*	35	10%	50	25-300mg
Olanzapine	28	8%	5	2.5-20mg
Risperidone	16	5%	0.5	0.25-3mg
Chlorpromazine	8	2%	50	12.5-100mg
Zuclopenthixol	7	2%	20	2-20mg
Promazine	6	2%	50	25-100mg
Aripiprazole	3	1%	10	5-10mg
Levomepromazine	3	1%	50	50-50mg

Of the 35 episodes where oral quetiapine was administered, 23 (66%) of these were for patients over 65 years old.

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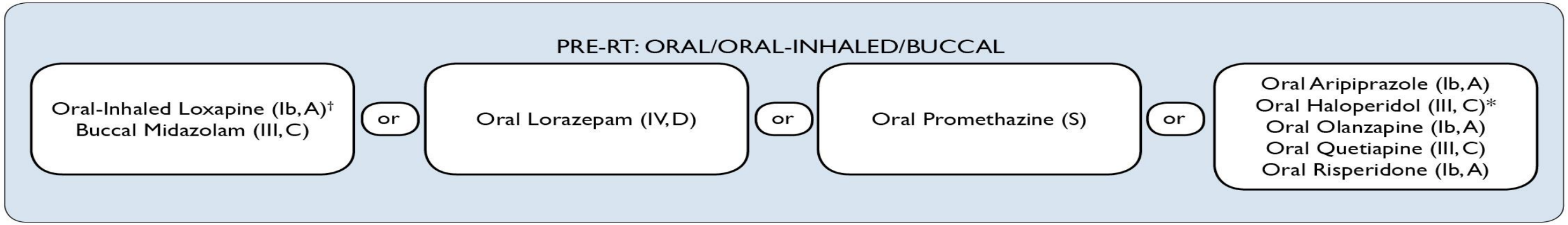
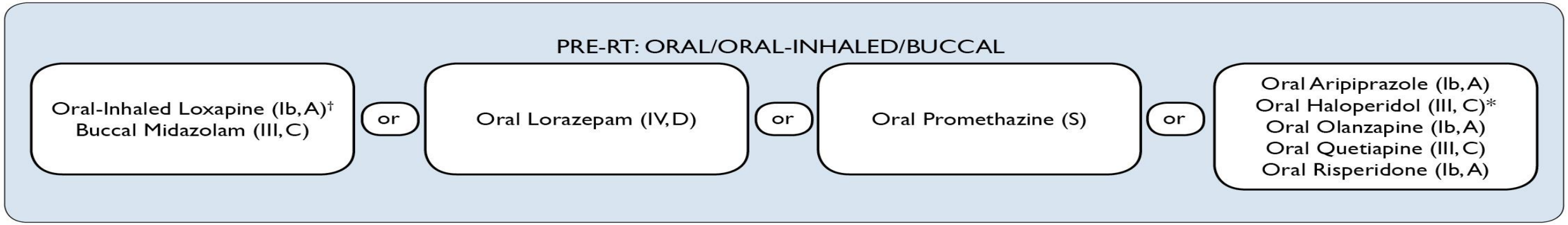
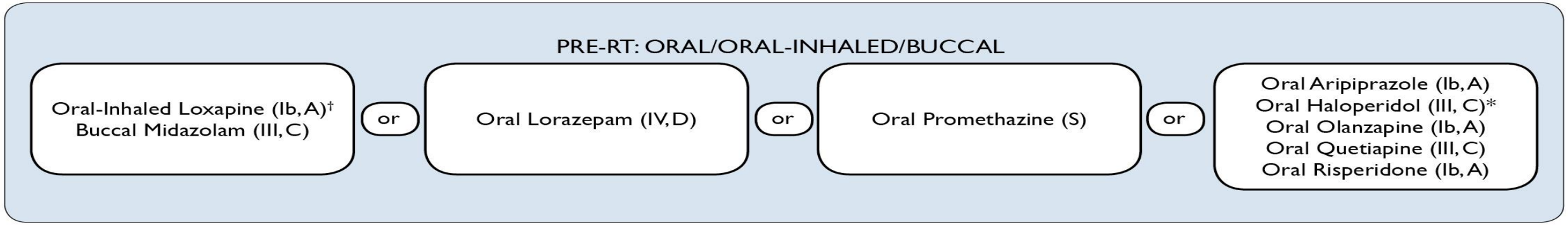


- Oral-inhaled **loxapine** is effective
  - although a brief respiratory assessment is required beforehand, as it is contraindicated in patients with asthma or chronic obstructive pulmonary disease, and a short-acting beta- agonist bronchodilator (e.g. salbutamol) should be available (Ib; A)
- Buccal **midazolam** is effective (III; C)
- Oral **lorazepam** may be effective (IV; D)
- Oral **promethazine** may be effective (S)



- Oral formulations of **aripiprazole**, **olanzapine** and **risperidone** are effective (Ib; A)
- Oral **haloperidol** is effective
  - a baseline ECG is advised before use due to the risk of QTc prolongation (III; C)
- Oral **quetiapine** is effective (III; C)



- Oral formulations of clonazepam and diazepam are not recommended
  - due to lack of evidence for use in RT together with the risk of accumulation with repeated dosing and the resultant risk of cumulative adverse effects (S)
- Oral levomepromazine is not recommended
  - due to lack of evidence for use in RT (S)

Summary

- Still gaps in evidence, but there *is* evidence to inform practice
- Aim of PRN oral medicines or "pre-RT" is to:
  - Pre-emptively address acute disturbance
  - To avoid escalation
  - To avoid the need for parenteral medication and physical restraint
- Minimal evidence of efficacy or safety - yet routine practice
  - Mixing and matching medicines: ?efficacy, ↑cumulative risks
- Specific choices (x9) influenced by evidence tailor to patient.

⇨**Main goal has to be to optimise the patients' regular treatment**