Gloucestershire Hospitals NHS Foundation Trust
Pharmacy

Gloucestershire Health and Care NHS Foundation Trust

Evidence for the use of oral and IM RT medication in acute disturbance

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Pharmacological management of acute disturbance
Friday 3rd November 2023

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RT Definitions & Concepts


NICE National Institute for Health and Care Excellence

NICE guideline

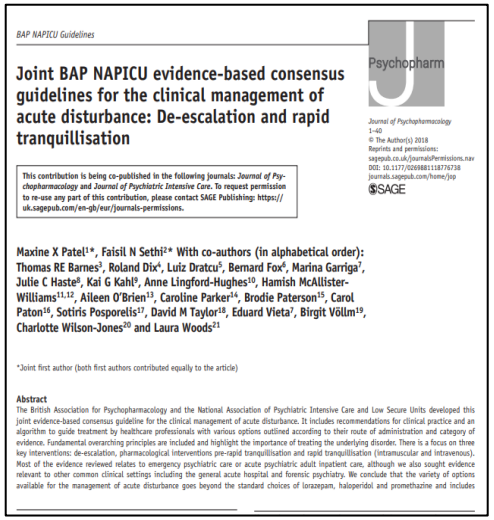
Violence and aggression: short-term management in mental health, health and community settings

NICE guideline
Published: 28 May 2015
www.nice.org.uk/guidance/ng10

Rapid tranquillisation

Rapid tranquillisation in this guideline refers to the use of medication by the parenteral route (usually intramuscular or, exceptionally, intravenous) if oral medication is not possible or appropriate and urgent sedation with medication is needed.

Defining rapid tranquillisation (RT) has been the subject of debate. The goal of RT is to achieve a state of calmness without sedation, sleep or unconsciousness, thereby reducing the risk to self and/or others while maintaining the ability of the patient to respond to communication (NICE, 2005). However, for acute disturbance, sedation may also be considered to be an appropriate interim strategy. Guidelines have also varied, with the key


BAP NAPICU Guidelines

Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation

Psychopharm

Journal of Psychopharmacology
1–40
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Maxine X Patel[1]*, Faisil N Sethi[2]* With co-authors (in alphabetical order): Thomas RE Barnes[3], Roland Dix[4], Luiz Dratcu[5], Bernard Fox[6], Marina Garriga[7], Julie C Haste[8], Kai G Kahl[9], Anne Lingford-Hughes[10], Hamish McAllister-Williams[11,12], Aileen O'Brien[13], Caroline Parker[14], Brodie Paterson[15], Carol Paton[16], Sotiris Posporelis[17], David M Taylor[18], Eduard Vieta[7], Birgit Völlm[19], Charlotte Wilson-Jones[20] and Laura Woods[21]

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Abstract

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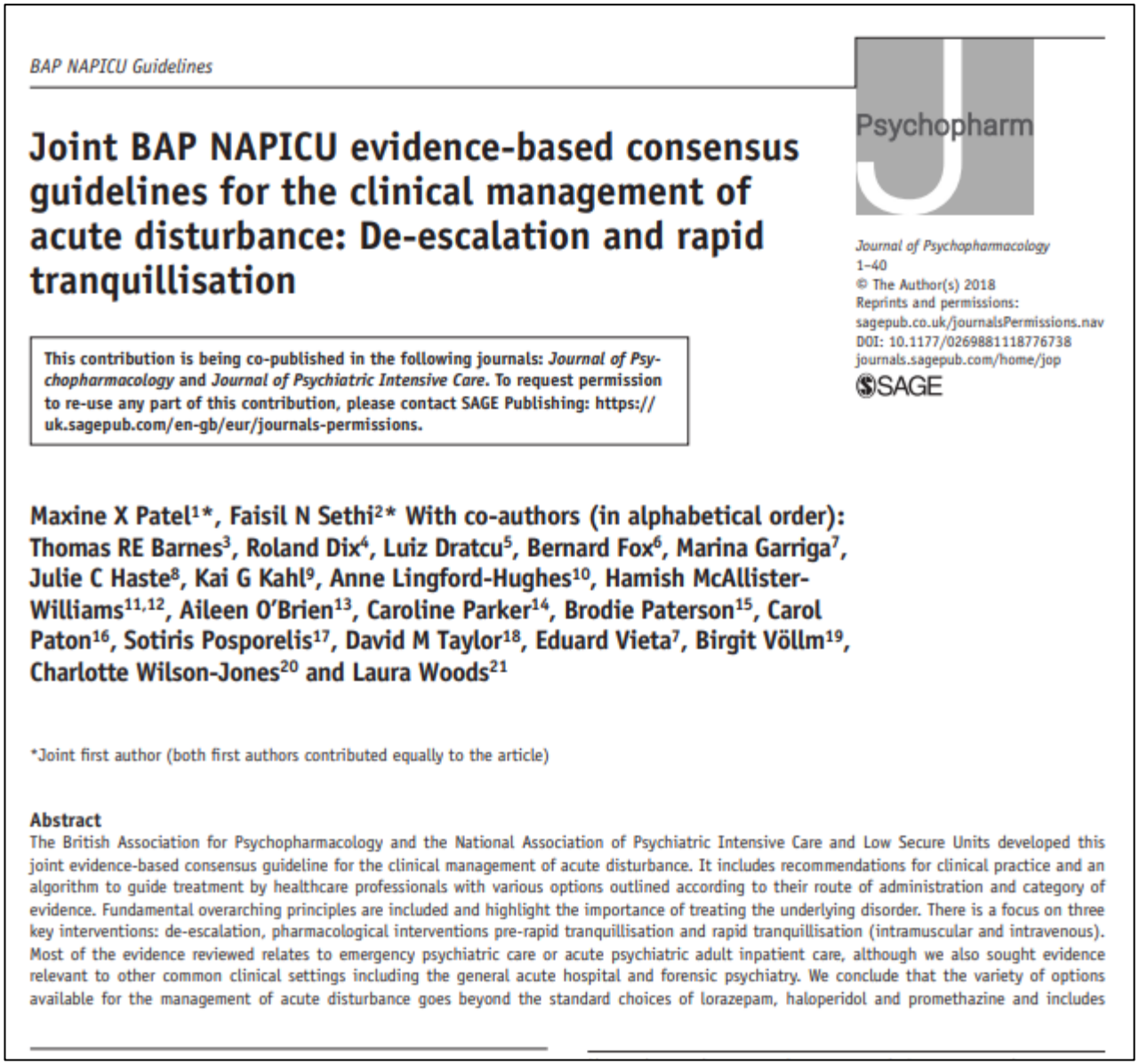
NAPICU / BAP guidance



BAP NAPICU Guidelines

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BAP_Guidelines-RapidTranquillisation.pdf

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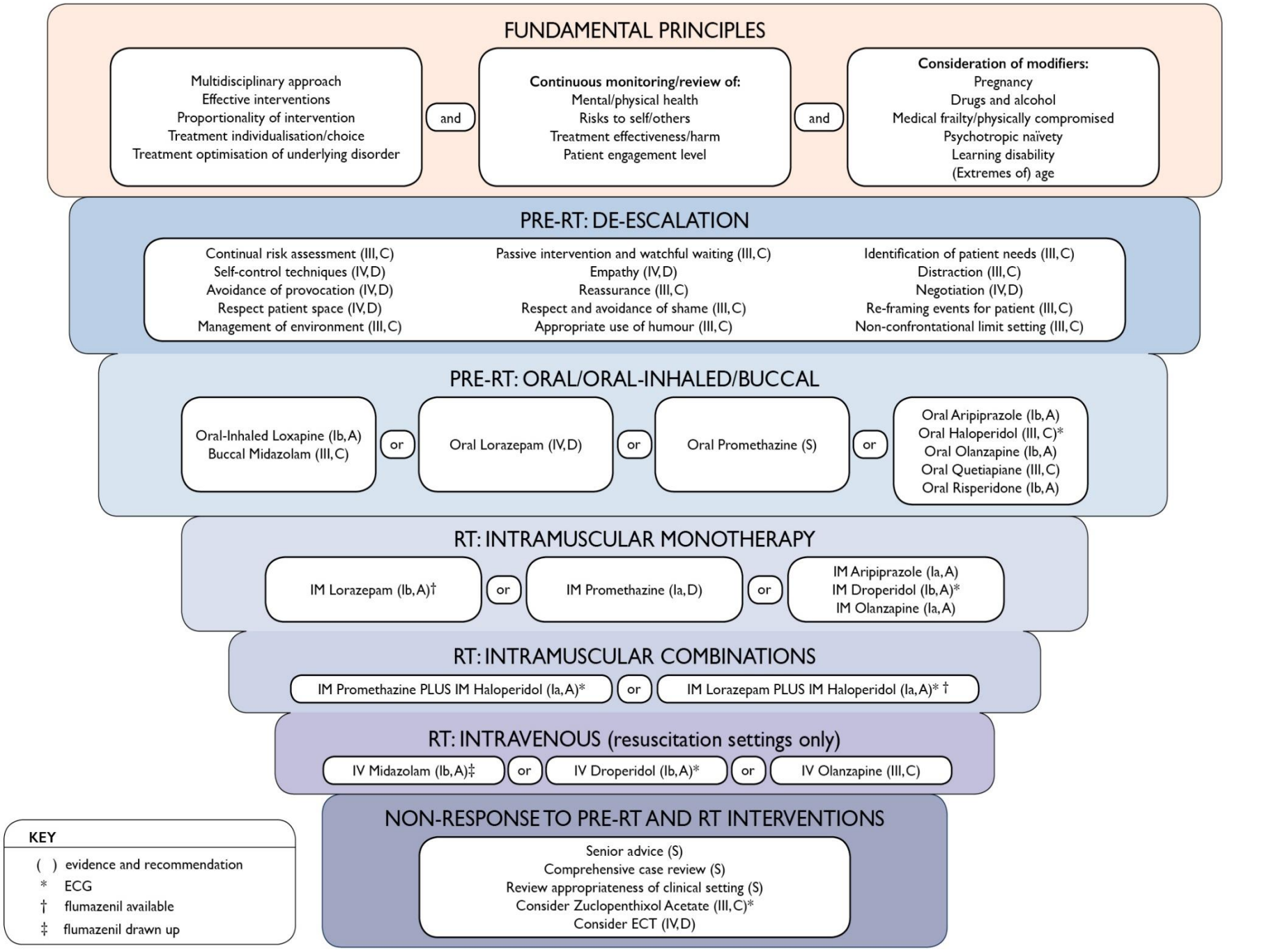
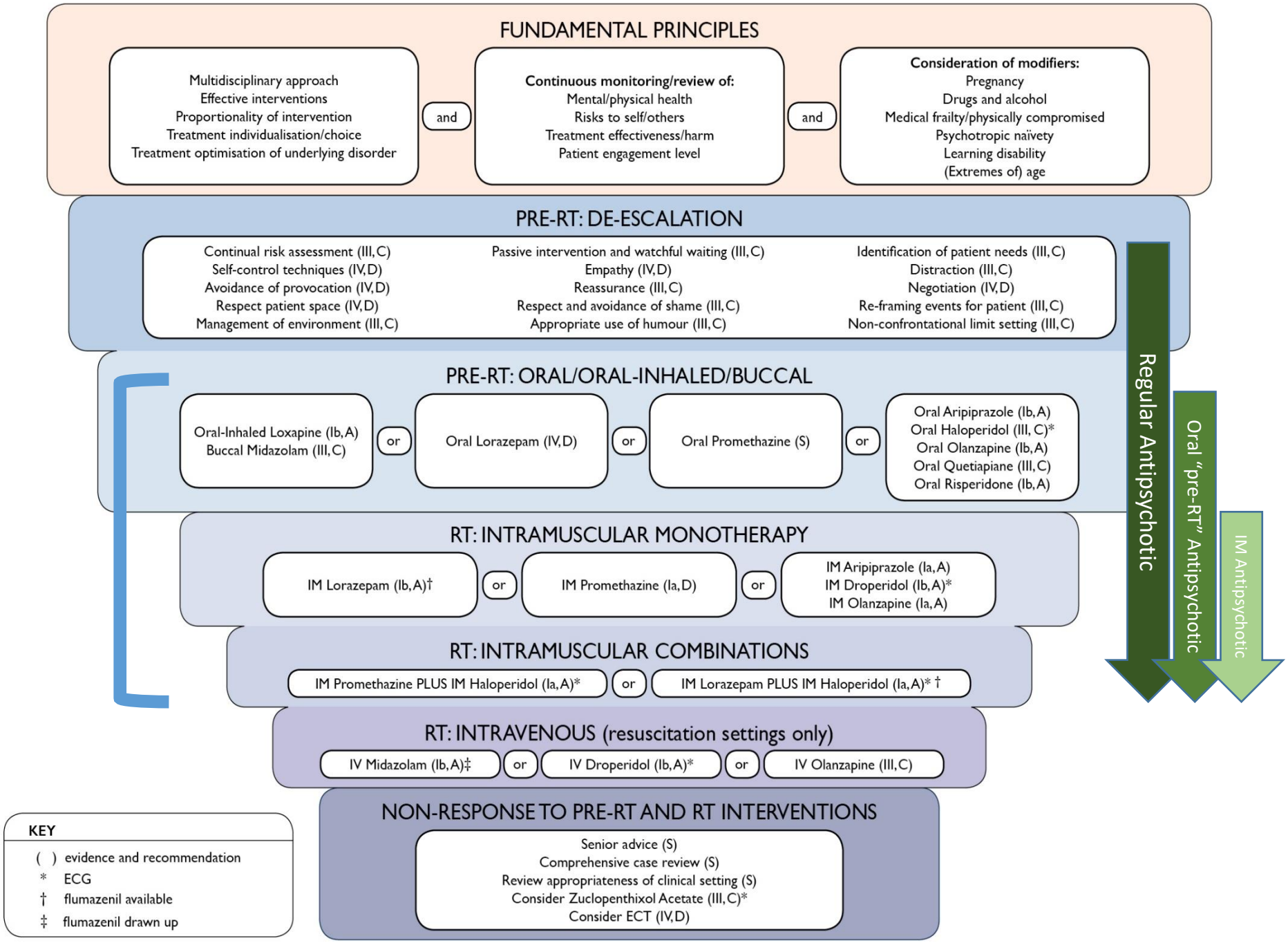

FUNDAMENTAL PRINCIPLES
Multidisciplinary approach
Effective interventions
Proportionality of intervention
Treatment individualisation/choice
Treatment optimisation of underlying disorder
and
Continuous monitoring/review of:
Mental/physical health
Risks to self/others
Treatment effectiveness/harm
Patient engagement level
and
Consideration of modifiers:
Pregnancy
Drugs and alcohol
Medical frailty/physically compromised
Psychotropic naïvety
Learning disability
(Extremes of) age
PRE-RT: DE-ESCALATION
Continual risk assessment (III, C)
Self-control techniques (IV, D)
Avoidance of provocation (IV, D)
Respect patient space (IV, D)
Management of environment (III, C)
Passive intervention and watchful waiting (III, C)
Empathy (IV, D)
Reassurance (III, C)
Respect and avoidance of shame (III, C)
Appropriate use of humour (III, C)
Identification of patient needs (III, C)
Distraction (III, C)
Negotiation (IV, D)
Re-framing events for patient (III, C)
Non-confrontational limit setting (III, C)
PRE-RT: ORAL/ORAL-INHALED/BUCCAL
Oral-Inhaled Loxapine (Ib, A)
Buccal Midazolam (III, C)
or
Oral Lorazepam (IV, D)
or
Oral Promethazine (S)
or
Oral Aripiprazole (Ib, A)
Oral Haloperidol (III, C)*
Oral Olanzapine (Ib, A)
Oral Quetiapiane (III, C)
Oral Risperidone (Ib, A)
RT: INTRAMUSCULAR MONOTHERAPY
IM Lorazepam (Ib, A)†
or
IM Promethazine (Ia, D)
or
IM Aripiprazole (Ia, A)
IM Droperidol (Ib, A)*
IM Olanzapine (Ia, A)
RT: INTRAMUSCULAR COMBINATIONS
IM Promethazine PLUS IM Haloperidol (Ia, A)*
or
IM Lorazepam PLUS IM Haloperidol (Ia, A)* †
RT: INTRAVENOUS (resuscitation settings only)
IV Midazolam (Ib, A)‡
or
IV Droperidol (Ib, A)*
or
IV Olanzapine (III, C)
NON-RESPONSE TO PRE-RT AND RT INTERVENTIONS
Senior advice (S)
Comprehensive case review (S)
Review appropriateness of clinical setting (S)
Consider Zuclopenthixol Acetate (III, C)*
Consider ECT (IV, D)
KEY
( ) evidence and recommendation
* ECG
† flumazenil available
‡ flumazenil drawn up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Regular Antipsychotic
Oral "pre-RT" Antipsychotic
IM Antipsychotic
KEY
( ) evidence and recommendation
* ECG
† flumazenil available
‡ flumazenil drawn up

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

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

Authors' conclusions:

There is currently no evidence from within randomised trials to support this common practice. Current practice is based on clinical experience and habit rather than high quality evidence.

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

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Evidence of efficacy for oral benzos

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

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

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Evidence for oral antipsychotics (1)

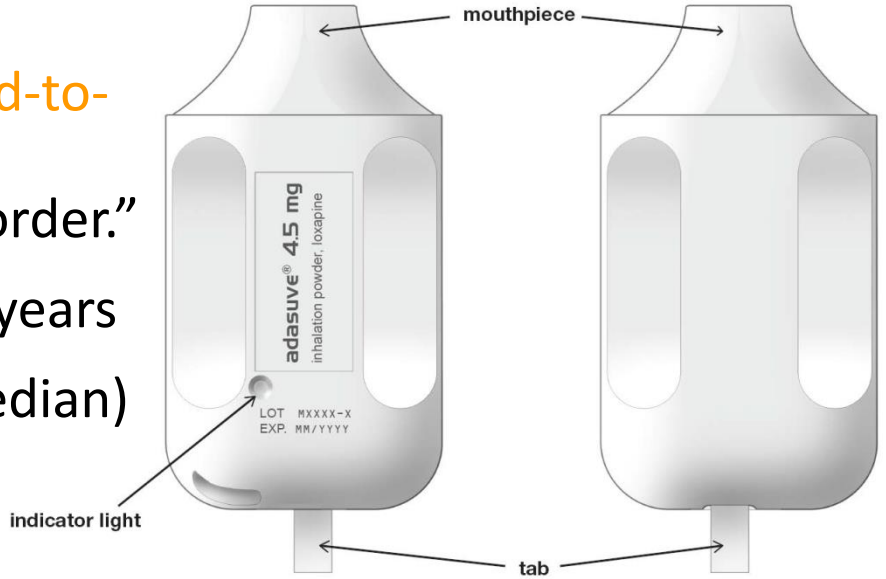
- **Olanzapine**:
  - Oro-dispersible **olanzapine** vs **risperidone** liquid (n = 87), equally effective in reducing PANSS-EC scores, no difference in need for additional injections (Hatta et al., 2008)
  - Oral **olanzapine** vs **oral aripiprazole** RCT 5-days (n = 604): significant improvements 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** vs **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** vs **IM FGAs +/-IM lorazepam** (n=226) and found oral risperidone+ oral lorazepam more successful at 2hrs plus less EPS than with IMs (Lejeune 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 2010)

Evidence for oral antipsychotics (2)

- **Quetiapine**
  - 5-day study (n = 36) suggested effectiveness, mean OAS scores reduced (Ganesan 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 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 for "the management of mild-to-moderate agitation in adults with schizophrenia or bipolar affective disorder."
- Typical: Used oral & IM in Europe for years
- 10mg inhaled Tmax: **1.13minutes** (median)
- $t_{1/2}$: mean 7 - 8 hours



- Most common AEs:
  Dysgeusia, throat irritation, few cases of EPS (dystonia, akathisia)
- Contraindicated in asthma and COPD, or other lung diseases associated with broncho-spasm, or lung diseases with acute respiratory symptoms
- No effects on the cardiovascular system

Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine*

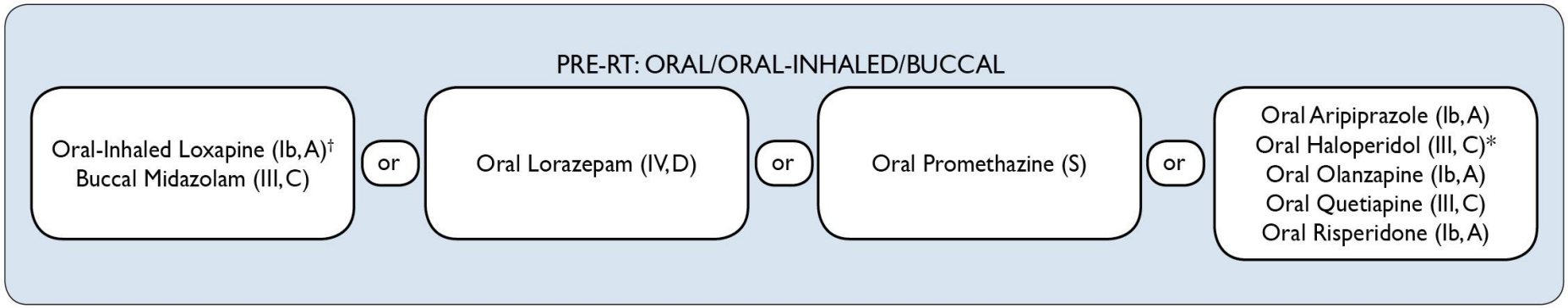
Michael D. Lesem, Tram K. Tran-Johnson, Robert A. Riesenberg, David Feifel, Michael H. Allen, Robert Fishman, Daniel A. Spyker, John H. Kehne and James V. Cassella

The British Journal of Psychiatry (2011)198, 51–58

Evidence for oral 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



- 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)

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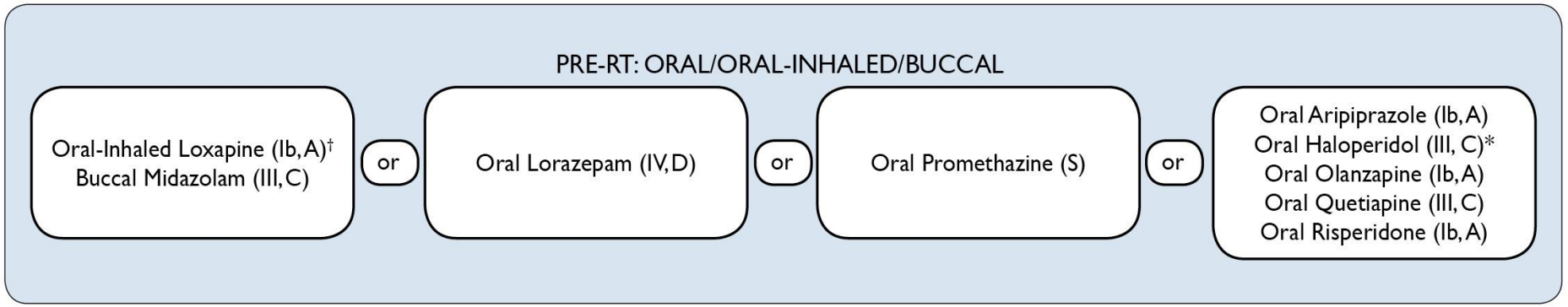

- Oral formulations of **aripiprazole**, **olanzapine** and **risperidone** are effective (Ib; A)
- Oral **haloperidol** is effective
  - a baseline ECG is advised before use due to the risk of QTc prolongation (III; C)
- Oral **quetiapine** is effective (III; C)

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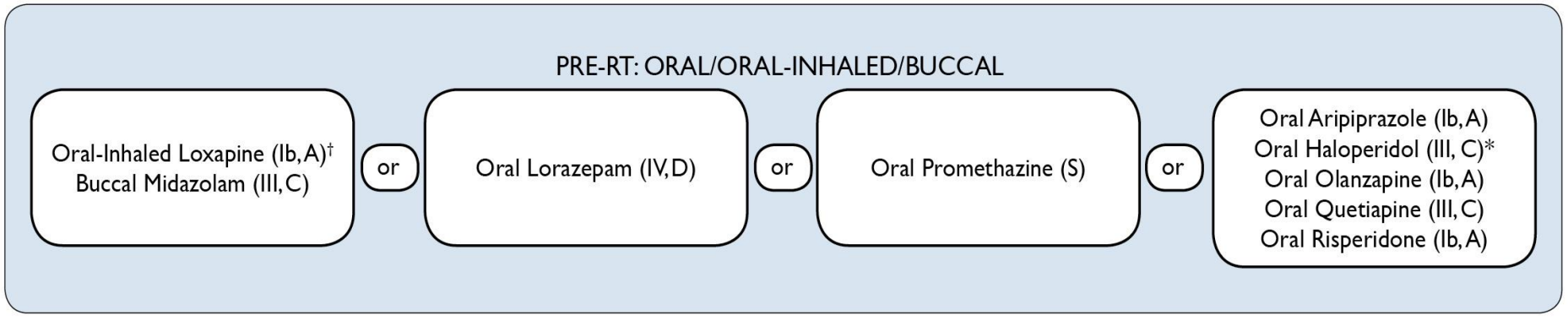

- Oral formulations of clonazepam and diazepam are not recommended
  - due to lack of evidence for use in RT together with the risk of accumulation with repeated dosing and the resultant risk of cumulative adverse effects (S)
- Oral levomepromazine is not recommended
  - due to lack of evidence for use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

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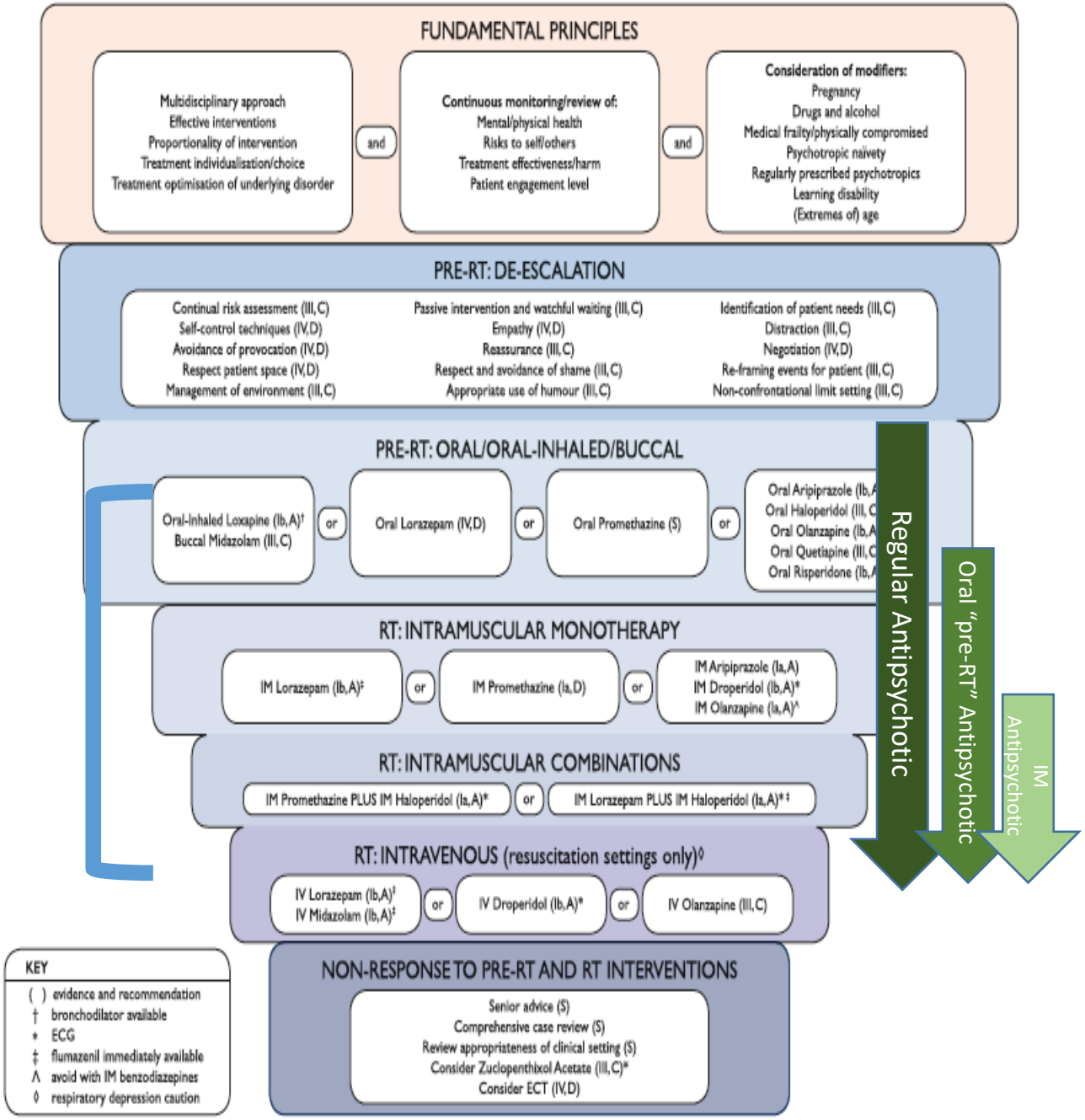
Summary: Orals

- 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**



Medicines for Rapid Tranquillisation

Drug	Route	Time to start of effect	Time to peak effect	Duration of effect	Reversing agent
Aripiprazole	IM	30-45mins	1-3hrs	18-24 hours	None
Diazepam	IV	5-10 seconds	< 1min	12-24 hours	Flumazenil
Haloperidol	Oral	1-2hrs	2-6hrs	18-24 hours	None
	IM	15-30mins	20mins		
Lorazepam	Oral	20-30mins	2hrs	6-8hrs	Flumazenil
	IM	15-30mins	60-90mins		
Olanzapine	Oral	~2 hrs	5 – 8hrs	24 hours	None
	IM	15-30mins	15-45mins		
Promethazine	Oral	~2 hrs (15-30mins)	2-3 hrs	12 hours (4-6hrs)	None
	IM	30-60mins	1-2 hrs	10 hours (2-8hrs)	
Midazolam	IM	5-20mins	5-20mins	?few hours	Flumazenil
Risperidone	Oral	30-60mins	1-2hrs	12-24 hours	None
Zuclopenthixol Acetate	IM	2 hours	6 -12 hrs	24-36 hours	None

RT Evidence - Benzos or Antipsychotics?

Benzodiazepines for psychosis-induced aggression or agitation

Donna Gillies[1], Alison Beck[2], Annie McCloud[3], John Rathbone[4]

[1]Sydney West Area Mental Health Service, Parramatta BC, Australia. [2]Shaftesbury Clinic, Springfield Hospital, London, UK. [3]Specialist Addiction Unit, East London & the City Mental Health NHS Trust, London, UK. [4]Cochrane Schizophrenia Group, Institute of Mental Health, Nottingham, UK

Contact address: Donna Gillies, Sydney West Area Mental Health Service, Cumberland Hospital, Locked Bag 7118, Parramatta BC, NSW, 2150, Australia. Donna_Gillies@wsahs.nsw.gov.au.

Editorial group: Cochrane Schizophrenia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 5, 2010.
Review content assessed as up-to-date: 4 August 2005.

Citation: Gillies D, Beck A, McCloud A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003079. DOI: 10.1002/14651858.CD003079.pub2.

21 trials, any benzo, any route, n=1,968, trial duration: 1hr-2wks

Benzos ≈ Antipsychotics

Benzos+Antipsychotics ≈ Benzos ≈ Antipsychotics

Benzos+Haloperidol < Olanzapine

Midazolam+Haloperidol > Olanzapine

Only parenteral benzodiazepines
No head-to-head benzo studies

Lorazepam (1971)

- Short acting benzodiazepine, no active metabolite
  - low risk of accumulation
- Bio-equivalent (no first pass hepatic effect): po = IM
- Onset of action IM: 15-30mins (po: 20-30mins)
- Peak IM: 60-90 minutes (po: 2 hours)
- t½ : 12-16 hours, duration effect: 6-8 hours
- ***Flumazenil*** - benzodiazepine antagonist IV administration

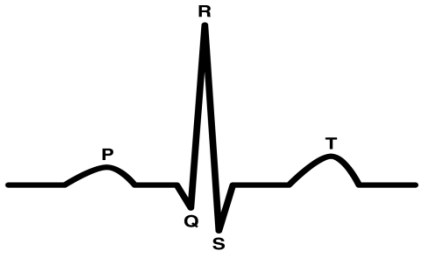
Qu. Maximum dose IM?

License: "Acute Anxiety

Adults: 0.025-0.03mg/kg (1.75-2.1mg for an average 70kg man). Repeat 6 hourly"

Lorazepam Macure 4mg/ml solution for injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Haloperidol (1959)



- Bioequivalence: 10mg po = 6mg IM
- Onset of action IM: 15-30mins, (po: 1-2 hours)
- Peak IM:20 minutes (po: peak 2-6 hours)
- t½ 21 hours, duration effect 18-24 hours
- ↑ECG monitoring requirements
- SPC: "*Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination…… discontinue if the QTc exceeds 500ms*."
- QTc prolongations is dose related
  - BNF maximums now **20mg/d po, 12mg/d IM**
- Concomitant use of other drugs that ↑QT interval may ↑risk

Olanzapine IM injection (2001)

- Onset of action IM: 15-30mins (po: ~ 2 hours)
- Peak 15-45 minutes (po peak: 5-8 hours), Cmax is 5x that of po
- t½: 30 hours, duration of effect: ~24 hours

Dose: 10mg, PO = IM

- Injections must be >2 hrs apart, max 3 inj **or** 20mg/24hrs all routes

Fatalities – **8** when used outside of SPC

Cardiorespiratory depression, hypotension + bradycardia

"Common" (1-10%): Bradycardia, with or without hypotension or syncope, tachycardia (SPC).

"Simultaneous injection of IM olanzapine and parenteral benzodiazepine is not recommended. If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least 1 hour after IM olanzapine administration."

Good option if concerned about EPS / antipsychotic naive

- Still licensed in EU
- No longer marketed or distributed by Lilly in UK
  (Financial reasons (not clinical) - Can be imported

Aripiprazole IM injection▼ (2007)

- Onset of action IM: 30-45mins (slower)
- Peak levels at 1-3 hours
- t½ = 75 hours
- Dose: **9.75mg = 1.3mls**
  - Inj must be at least 2 hrs apart
  - max. 3 inj **or** 30mg/24hrs all routes

✓ With concurrent benzodiazepines

- Less effective than haloperidol
- "*Common*" side effects (1-10%):
  - Somnolence - Dizziness
  - Headache - Akathisia
  - Nausea - Vomiting

Common Side Effects with oral
- Headache (31.7%)
- Insomnia (24.1%)
- Nausea & vomiting (12-14%)
- Light-headedness (11.4%)
- Akathisia (<10%)
- Somnolence (<10%)
- Constipation & dyspepsia (<10%)
- Blurred vision (<10%)
- Tachycardia (<1%),
- Orthostatic hypotension (<1%)

Citrome L. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. *J Clin Psych.* 2007; **68:** 1876-1885.

Promethazine IM

- An antihistamine with sedative properties
- Licensed indications:

  "Sedation & treatment of insomnia in adults"

- TREC trials x4, ***with*** haloperidol
- An option when lorazepam cannot be used:
  - e.g. patient is tolerant / addicted
  - Cannot tolerate benzos e.g. severe respiratory disease

- Slower onset of action **1-2 hours** (Oral peaks at 2-3 hours)
- t½ 7-15 hours, effects last 4–6 hours but may persist for 12 hours after oral administration (= good as a hypnotic)
- Dose: 25-50mg, max 100mgs
- No studies evaluated the use of oral or IM monotherapy as RT
- No evidence to recommend efficacy or safety concurrently ***with*** **lorazepam – not recommended** (BAP/NAPICU)

Midazolam IM

- Quick onset of action[1,2] rapid & complete absorption
- Short duration of action
- Risks – **respiratory depression** (> lorazepam)
- Flumazenil (Dr to administer)
- CQC advice to SOADs, unlicensed indication
- Legal practicalities: Controlled Drug (Schedule 4)
- **Not recommended – safety concerns**

1. Huf G *et al*. Rapid tranquillisation for agitated patients in psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *British Medical Journal* 2003; 327 (7417): 708-711
2. Martel M., Sterzinger A, Miner J, *et al*. Management of acute undifferentiated agitation in the emergency department: A randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Academic Emergency Medicine*. 2005; 12 (12): 1167-1172.

Droperidol IM

- First generation antipsychotic: butyrophenone
  - similar pharmacology to haloperidol, but more sedative

QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients

J G Reilly, S A Ayis, I N Ferrier, S J Jones, S H L Thomas

Summary

Background Sudden unexplained death in psychiatric patients may be due to drug-induced arrhythmia, of which lengthening of the rate-corrected QT interval (QTc) on the electrocardiogram is a predictive marker. We estimated the point prevalence of QTc lengthening in psychiatric patients and the effects of various psychotropic drugs.

Methods Electrocardiograms were obtained from 101 healthy reference individuals and 495 psychiatric patients in various inpatient and community settings and were analysed with a previously validated digitiser technique. Patients with and without QTc lengthening, QTc dispersion, and T-wave abnormality were compared by logistic regression to calculate odds ratios for predictive variables.

Findings Abnormal QTc was defined from the healthy reference group as more than 456 ms and was present in 8% (40 of 495) of patients. Age over 65 years (odds ratio 3·0 [95% CI 1·1–8·3]), use of tricyclic antidepressants (4·4 [1·6–12·1]), thioridazine (5·4 [2·0–13·7]), and droperidol (6·7 [1·8–24·8]) were robust predictors of QTc lengthening, as was antipsychotic dose (high dose 5·3 [1·2–24·4]; very high dose 8·2 [1·5–43·6]). Abnormal QT dispersion or T-wave abnormalities were not significantly associated with antipsychotic treatment, but were associated with lithium therapy.

Interpretation Antipsychotic drugs cause QTc lengthening in a dose-related manner. Risks are substantially higher for thioridazine and droperidol. These drugs may therefore confer an increased risk of drug-induced arrhythmia.

Lancet 2000; **355:** 1048–52

Introduction

Cardiovascular mortality in psychiatric patients is high.[1] Reports of sudden unexplained death in those taking antipsychotic drugs[2,3] have raised the concern that part of this excess may be due to drug-induced arrhythmias, since many of these drugs have cardiac electrophysiological effects similar to those of quinidine.[2] The polymorphic ventricular arrhythmia known as torsade de pointes has been recorded in patients with psychotropic drug overdose[4] and provides a plausible mechanism for sudden unexplained death associated with drug therapy.[5]

Several psychotropic drugs are associated with lengthening of the rate-corrected QT interval (QTc) on the electrocardiogram,[2] which often precedes torsade.[6] There is no direct evidence linking the extent of drug-induced QTc lengthening with the risk of torsade or sudden death. However, QTc-interval lengthening is a predictor of sudden death in patients with cardiac disease[7] and the extent of drug-induced QTc-interval lengthening is thought to be an important marker of arrhythmia risk by drug regulatory authorities (see website: www.emeasearch.is.eudra.org/humandocs/PDFs/SWP/098696en.pdf). Risk of arrhythmia with drugs that lengthen ventricular repolarisation may also be indicated by the dispersion of repolarisation, which can be assessed by measuring QT dispersion.[8] Abnormal repolarisation may also cause non-specific abnormalities of the T wave, although there is no direct evidence to link such changes with arrhythmia.

Clinical guidelines advise caution in the use of high-dose antipsychotic therapy with special reference to the risk of sudden death, as well as regular monitoring of the QTc interval,[9] but evidence for this change in practice is

CMHP
College of Mental Health Pharmacy

napicu
national association of psychiatric intensive care & low secure units

Droperidol IM

- A subsequently further blinded RCTs in Australian PICUs
- IM droperidol 10mg (n = 118) vs IM haloperidol 10mg (n = 110), median time to sedation was 20 minutes for IM haloperidol and 25 minutes for IM droperidol (not statistically significant[1]
- More additional sedation was needed with IM haloperidol
- More adverse effects (hypotension) with IM droperidol
- Cochrane review[2] of IM/IV: droperidol is effective and can be used as RT

1. Calver L, Page CB, Downes MA, et al. (2015a) The safety and effectiveness of droperidol for sedation of acute behavioural disturbance in the emergency department. Ann Emerg Med 66: 230–238.
2. Khokhar MA and Rathbone J (2016) Droperidol for psychosisinduced aggression or agitation (review). Cochrane Database Syst Rev 12: CD002830.

Droperidol IM

Drug action

Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

Indications and dose

Prevention and treatment of postoperative nausea and vomiting

By intravenous injection

Adult
0.625–1.25 mg, dose to be given 30 minutes before end of surgery, then 0.625–1.25 mg every 6 hours as required.

Elderly
625 micrograms, dose to be given 30 minutes before end of surgery, then 625 micrograms every 6 hours as required.

Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia (PCA)

By intravenous injection

Adult
15–50 micrograms of droperidol for every 1 mg of morphine in PCA, reduce dose in elderly; maximum 5 mg per day.

Generating evidence

- Designing trials – difficult
  - Agree An Aim
    - slightly drowsy → comatose
  - Consent
  - Assessment measures

Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine

TREC Collaborative Group

Abstract

Objective To compare two widely used drug treatments for people with aggression or agitation due to mental illness.

Design Pragmatic, randomised clinical trial.

Setting Three psychiatric emergency rooms in Rio de Janeiro, Brazil.

Subjects 301 aggressive or agitated people.

Interventions Open treatment with intramuscular midazolam or intramuscular haloperidol plus promethazine.

in psychiatric settings are secondary to severe illnesses such as schizophrenia or substance misuse.[1] Guidelines recommend that patients should be calmed by use of words and reassurance, a diagnostic history acquired, and physical and laboratory tests completed before drug treatment is started.[2] However, the acute danger of the situation often makes this impossible, with histories hurried and fragmented, diagnoses speculative, and physical examination impossible. To ensure the safety of everyone involved, rapid tranquillisation of aggressive or violent patients may be unavoidable.

The drugs used in such situations should calm

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BMJ

RESEARCH

Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine

Gisele Huf, associate professor,[1] E S F Coutinho, professor,[2] C E Adams, associate professor,[3] for the TREC Collaborative Group

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gisele@ensp.fiocruz.br

doi:10.1136/bmj.39339.448819.AE

ABSTRACT

Objective To determine whether haloperidol alone results in swifter and safer tranquillisation and sedation than haloperidol plus promethazine.

Design Pragmatic randomised open trial (January-July 2004).

Setting Psychiatric emergency room, Rio de Janeiro, Brazil.

Participants 316 patients who needed urgent intramuscular sedation because of agitation, dangerous behaviour, or both.

Interventions Open treatment with intramuscular haloperidol 5-10 mg or intramuscular haloperidol 5-10 mg plus intramuscular promethazine up to 50 mg;

Trial registration Current Controlled Trials ISRCTN83261243.

INTRODUCTION

Agitated and violent behaviour can occur in many different clinical settings. It arises in 10% of psychiatric emergencies and is most commonly associated with psychosis or substance misuse.[1,2] For control of the acute phase, guidelines in the United States and United Kingdom recommend the use of intramuscular haloperidol, lorazepam, both combined, or olanzapine.[3,4] However, little information on comparative effectiveness or safety is available. Some people consider it prudent to routinely combine

BMJ

RESEARCH

Rapid tranquillisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine

Nirmal S Raveendran, lecturer,[1] Prathap Tharyan, professor,[2] Jacob Alexander, lecturer,[1] Clive Elliot Adams, associate professor,[3] for the TREC-India II Collaborative Group

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doi:10.1136/bmj.39341.608519.BE

ABSTRACT

Objective To compare the effect of intramuscular olanzapine with intramuscular haloperidol plus promethazine on rapid tranquillisation of agitated or violent people with mental illness.

Design Pragmatic, allocation concealed, randomised controlled trial.

Setting Emergency services of a general hospital psychiatry department in Vellore, south India.

Participants 300 adults with agitated or violent behaviour as a result of mental illness; 150 randomised to intramuscular olanzapine and 150 randomised to intramuscular haloperidol plus promethazine.

Interventions Open treatment with intramuscular olanzapine or intramuscular haloperidol plus promethazine.

Main outcome measures Primary outcome was proportion of patients who were tranquil or asleep at 15 minutes and 240 minutes. Secondary outcomes were tranquillising or sedating agitated or violent patients with mental illness but the combination resulted in fewer additional medical interventions within four hours of intervention.

Trial registration Clinical trials NCT00455234.

INTRODUCTION

About 15 million people in India are estimated to have serious mental disorders.[1] Agitated or violent behaviour, mostly as a result of serious mental illness and substance misuse,[2-4] constitutes around 10% of the reasons for use of emergency services worldwide. As rates of mental illness are similar worldwide[5] it is reasonable to presume that the management of aggressive or violent behaviour is an important problem and a mental health priority in low and middle income countries, where most of the world's people live, and particularly in countries with large populations, such as India.

Non-pharmacological strategies are recommended

BRITISH JOURNAL OF PSYCHIATRY (2004), 185, 63–69

Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting

Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine

JACOB ALEXANDER, PRATHAP THARYAN, CLIVE ADAMS, THOMAS JOHN, CARINA MOL and JONCY PHILIP

Background The pharmacological management of violence in people with psychiatric disorders is under-researched.

Aims To compare interventions commonly used for controlling agitation or violence in people with serious psychiatric disorders.

Method We randomised 200 people to receive intramuscular lorazepam (4 mg) or intramuscular haloperidol (10 mg) plus promethazine (25–50 mg mix).

Results At blinded assessments 4 h later (99.5% follow-up), equal numbers in

Violent or aggressive behaviour is a common reason for emergency psychiatric presentations, with assaultive behaviour seen in 3–10% of psychiatric patients (Tardiff & Sweillam, 1982; Tardiff & Koenigsberg, 1985). A haloperidol–promethazine mix is commonly used for rapid tranquillisation of agitated or violent patients in India and Brazil (Huf *et al*, 2002*a*). Promethazine is an antihistamine that adds to the sedative effect of haloperidol and prevents acute dystonic reactions otherwise common with the intramuscular use of haloperidol (Van Harten *et al*, 1999). As a haloperidol–promethazine mix had not been evaluated previously in the context of a randomised trial, two pragmatic trials were designed by the Tranquili-

Department of Psychiatry at the Christ Medical College, in Vellore in the south Indian state of Tamil Nadu. The majo of patients presenting to the psychia emergency services of this 1800-bed tea ing hospital were accompanied by fan members and were either brought direc or were referred by general practition in the town or adjoining towns and villa and from emergency services of this other hospitals.

Patient selection

Consecutive patients were assessed were eligible for trial entry if the attend physician felt that intramuscular sedat was clearly indicated because of agitati aggression or violent behaviour, and if physician did not feel that either one the interventions posed an additional for the patient. In keeping with prevai clinical practice in this country, cons was obtained from a responsible relativ patients refused, or lacked capacity to c sent to treatment by virtue of severe me illness. For this trial relatives were f informed and their written cons obtained; patients without a respons relative were excluded. This trial compa

TREC trials x4

1. Brazil, 2003 (BMJ). n=301. Tranquil/sedated at 20mins.
   IM Midazolam vs. IM Haloperidol+promethazine

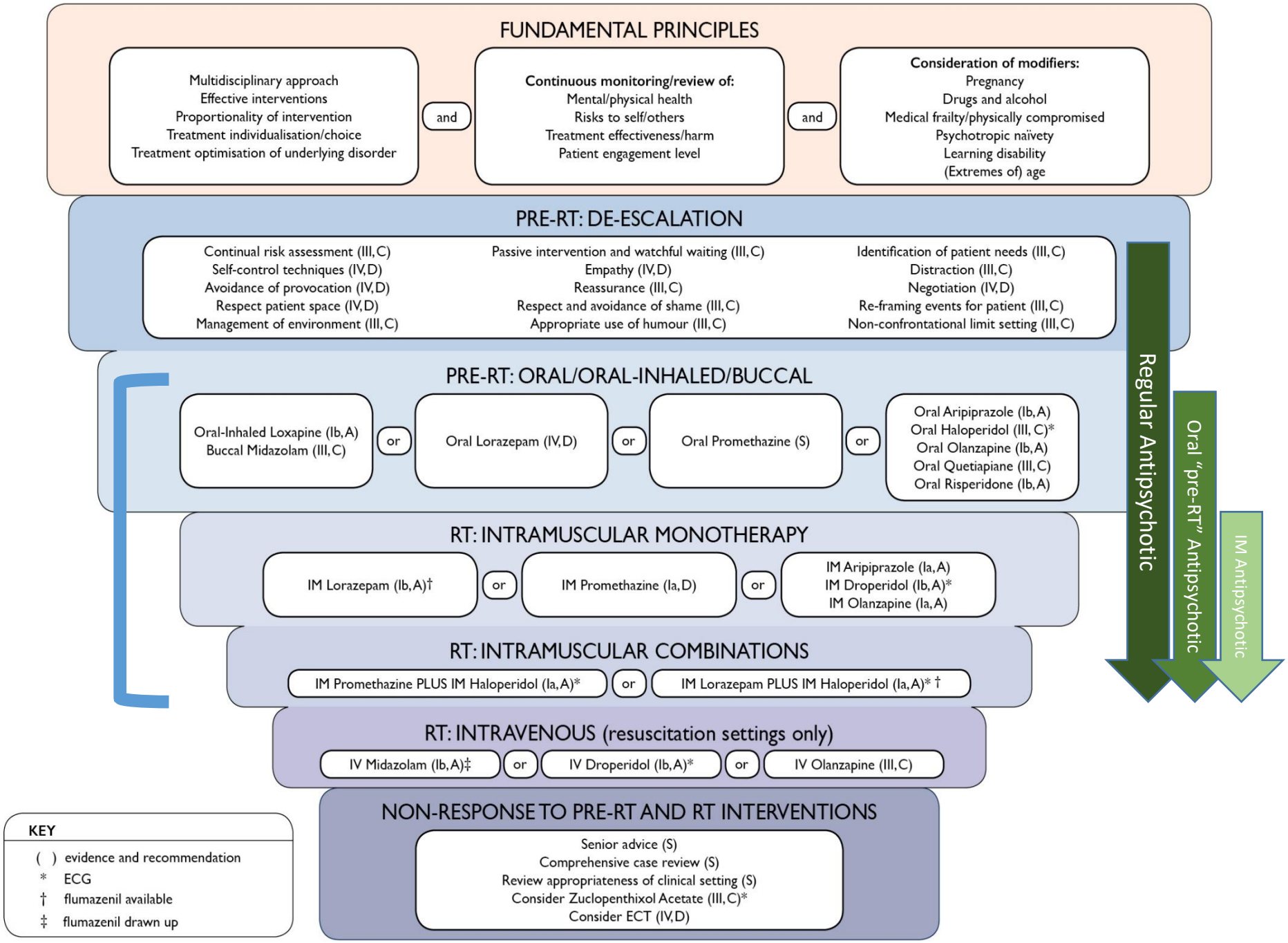
2. India, 2004 (BJPsych). n=200. Tranquil/asleep by 4hrs
   IM lorazepam vs. **IM Haloperidol+promethazine**

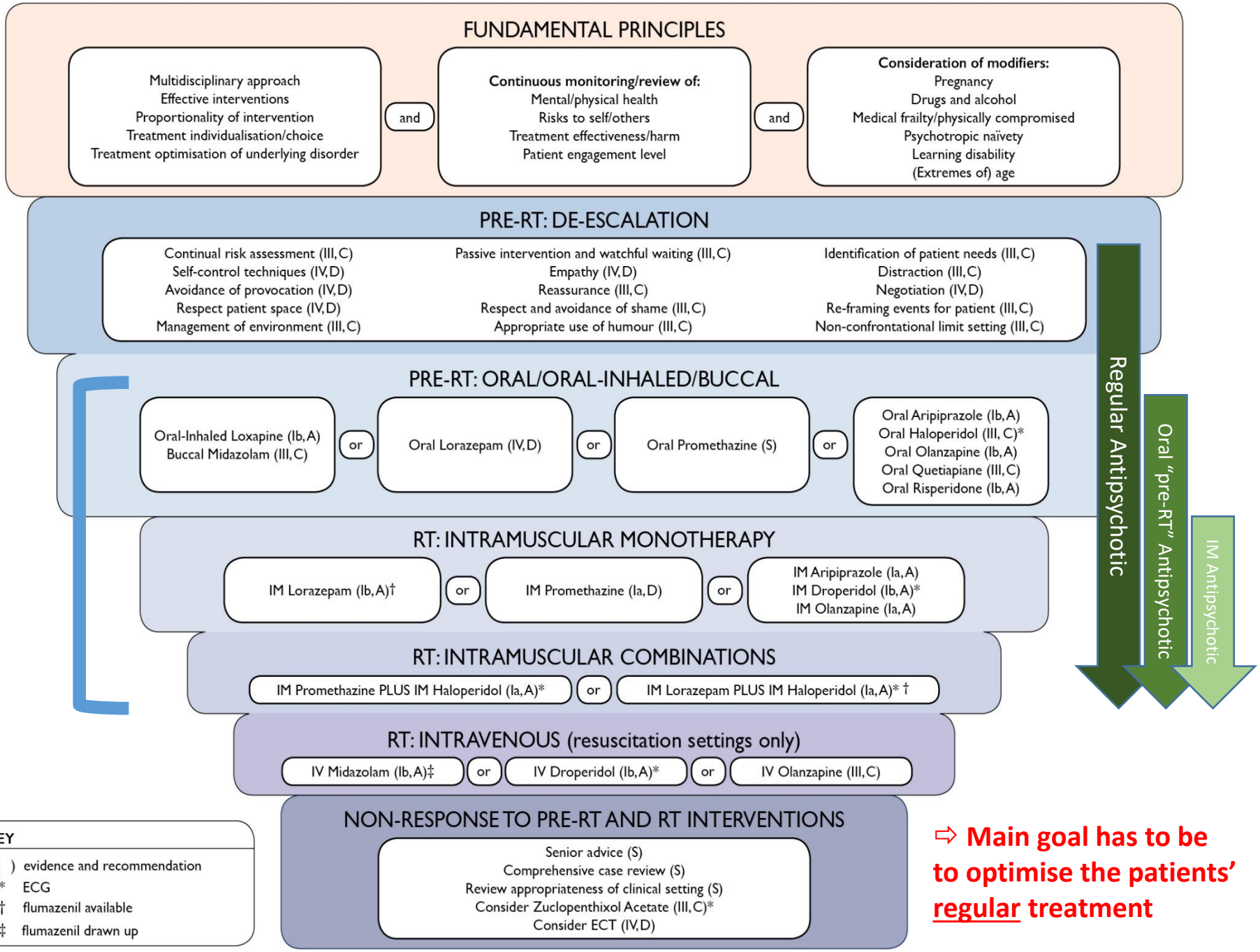
3. Brazil, 2007 (BMJ). n=316. Tranquil/asleep at 20mins.
   IM Haloperidol vs. **IM Haloperidol+promethazine**

4. India, 2007 (BMJ). n=300. Tranquil/asleep at 15mins.
   IM olanzapine vs. **IM Haloperidol+promethazine**

Evidence base challenges

- Evidence base is thin/weak, doesn't reflect UK practice
- TREC 1, Brazil *BMJ* 2003, n=301. **IM Midaz** superior to IM Halop+Promethaz, sedation @20mins.
- TREC 2, India *BJPsych* 2004, n=200. **IM Halop+Promethaz** superior to IM lorazepam, sedation @20mins.
- Point of assessments: e.g. 1hour!


FUNDAMENTAL PRINCIPLES
Multidisciplinary approach
Effective interventions
Proportionality of intervention
Treatment individualisation/choice
Treatment optimisation of underlying disorder
and
Continuous monitoring/review of:
Mental/physical health
Risks to self/others
Treatment effectiveness/harm
Patient engagement level
and
Consideration of modifiers:
Pregnancy
Drugs and alcohol
Medical frailty/physically compromised
Psychotropic naïvety
Learning disability
(Extremes of) age
PRE-RT: DE-ESCALATION
Continual risk assessment (III, C)
Self-control techniques (IV, D)
Avoidance of provocation (IV, D)
Respect patient space (IV, D)
Management of environment (III, C)
Passive intervention and watchful waiting (III, C)
Empathy (IV, D)
Reassurance (III, C)
Respect and avoidance of shame (III, C)
Appropriate use of humour (III, C)
Identification of patient needs (III, C)
Distraction (III, C)
Negotiation (IV, D)
Re-framing events for patient (III, C)
Non-confrontational limit setting (III, C)
PRE-RT: ORAL/ORAL-INHALED/BUCCAL
Oral-Inhaled Loxapine (Ib, A)
Buccal Midazolam (III, C)
or
Oral Lorazepam (IV, D)
or
Oral Promethazine (S)
or
Oral Aripiprazole (Ib, A)
Oral Haloperidol (III, C)*
Oral Olanzapine (Ib, A)
Oral Quetiapiane (III, C)
Oral Risperidone (Ib, A)
RT: INTRAMUSCULAR MONOTHERAPY
IM Lorazepam (Ib, A)†
or
IM Promethazine (Ia, D)
or
IM Aripiprazole (Ia, A)
IM Droperidol (Ib, A)*
IM Olanzapine (Ia, A)
RT: INTRAMUSCULAR COMBINATIONS
IM Promethazine PLUS IM Haloperidol (Ia, A)*
or
IM Lorazepam PLUS IM Haloperidol (Ia, A)* †
RT: INTRAVENOUS (resuscitation settings only)
IV Midazolam (Ib, A)‡
or
IV Droperidol (Ib, A)*
or
IV Olanzapine (III, C)
NON-RESPONSE TO PRE-RT AND RT INTERVENTIONS
Senior advice (S)
Comprehensive case review (S)
Review appropriateness of clinical setting (S)
Consider Zuclopenthixol Acetate (III, C)*
Consider ECT (IV, D)
Regular Antipsychotic
Oral "pre-RT" Antipsychotic
IM Antipsychotic
KEY
( ) evidence and recommendation
* ECG
† flumazenil available
‡ flumazenil drawn up


FUNDAMENTAL PRINCIPLES
Multidisciplinary approach
Effective interventions
Proportionality of intervention
Treatment individualisation/choice
Treatment optimisation of underlying disorder
and
Continuous monitoring/review of:
Mental/physical health
Risks to self/others
Treatment effectiveness/harm
Patient engagement level
and
Consideration of modifiers:
Pregnancy
Drugs and alcohol
Medical frailty/physically compromised
Psychotropic naïvety
Learning disability
(Extremes of) age
PRE-RT: DE-ESCALATION
Continual risk assessment (III, C)
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PRE-RT: ORAL/ORAL-INHALED/BUCCAL
Oral-Inhaled Loxapine (Ib, A)
Buccal Midazolam (III, C)
or
Oral Lorazepam (IV, D)
or
Oral Promethazine (S)
or
Oral Aripiprazole (Ib, A)
Oral Haloperidol (III, C)*
Oral Olanzapine (Ib, A)
Oral Quetiapiane (III, C)
Oral Risperidone (Ib, A)
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or
IM Promethazine (Ia, D)
or
IM Aripiprazole (Ia, A)
IM Droperidol (Ib, A)*
IM Olanzapine (Ia, A)
RT: INTRAMUSCULAR COMBINATIONS
IM Promethazine PLUS IM Haloperidol (Ia, A)*
or
IM Lorazepam PLUS IM Haloperidol (Ia, A)* †
RT: INTRAVENOUS (resuscitation settings only)
IV Midazolam (Ib, A)‡
or
IV Droperidol (Ib, A)*
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IV Olanzapine (III, C)
NON-RESPONSE TO PRE-RT AND RT INTERVENTIONS
Senior advice (S)
Comprehensive case review (S)
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Consider Zuclopenthixol Acetate (III, C)*
Consider ECT (IV, D)
Regular Antipsychotic
Oral "pre-RT" Antipsychotic
IM Antipsychotic
KEY
( ) evidence and recommendation
* ECG
† flumazenil available
‡ flumazenil drawn up
⇨ Main goal has to be to optimise the patients' regular treatment

with you, for you

NHS
Gloucestershire Health and Care
NHS Foundation Trust

Thank you for listening

Any questions?

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Rapid tranquillisation of the acutely disturbed patient

Author(s):
Dr Aileen O'Brien, Caroline Parker and Jules Haste

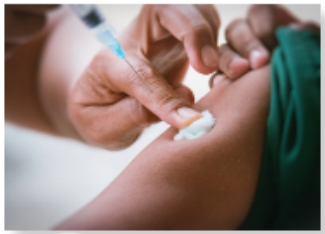
Duration:
90 minutes

Credits:
1.5

Published:
August 2022

Type:
Learning module

CPD domain:
Clinical



Module

This is a substantial revision of a previous module by Dr Stephen Pereira, Dr Deepak Garg and Dr David Branford. The authors acknowledge their contribution.

Disturbed or violent behaviour by an individual in an in-patient psychiatric setting poses a serious risk to that individual, other patients and staff.

Immediate management of such situations is necessary to ensure the safety of other patients and staff and to reduce the patient's level of distress.

Although non-pharmacological and oral pharmacological solutions should be attempted first, sometimes rapid tranquilisation (RT) is required.

NICE (2015) and BAP guidelines define rapid tranquillisation as 'the use of medication by the parenteral route if oral medication is not possible or appropriate and urgent sedation with medication is needed'.

The interventions used should be the minimum required to calm the patient.

Midazolam – buccal & sublingual

- Studied in paeds & LD - emergency antiepileptic, instead of rectal diazepam[1]
- Sublingual: high bioavailability (~75%) reliable plasma concs[2]
- Buccolam™ for oromucosal use, a pre-filled syringe
  - Solution should be slowly inserted into the space between the cheek and gum, approximately ½ the solution on each side of the mouth
  - *Only* licensed for treatment of seizures in < 18s, not in adults, not for RT
- One study (n=27)[3] in x2 English male PICUs, instead of IM, 6/12
  - Sedative effects at the first time point (15 minutes) peaking at 30 minutes, and lasted at least 1 hour (no further measures taken)
  - >1/3 further doses of RT were required within 24 hours
  - One case of oversedation
- **Poor evidence to recommended**

1. Sweetman S. Martindale: The complete drug reference (2013). The Pharmaceutical Press.
2. Schwagmeier R, et al. *Br J Clin Pharmacol* 1998; 46: 203–6
3. Taylor D, Okocha C, Paton C, Smith S, Connolly A. *Int J Psych Clin Prac*. 2008; **12** (4): 309-311