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

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**Maxine X Patel<sup>1,\*</sup>, Faisil N Sethi<sup>2,\*</sup>, Thomas RE Barnes<sup>3</sup>, Roland Dix<sup>4</sup>, Luiz Dratcu<sup>2</sup>, Bernard Fox<sup>5</sup>, Marina Garriga<sup>6</sup>, Julie C Haste<sup>7</sup>, Kai G Kahl<sup>8</sup>, Anne Lingford-Hughes<sup>3,9</sup>, Hamish McAllister-Williams<sup>10,11</sup>, Aileen O'Brien<sup>12,13</sup>, Caroline Parker<sup>14</sup>, Brodie Paterson<sup>15</sup>, Carol Paton<sup>16</sup>, Sotiris Posporelis<sup>17,18</sup>, David M Taylor<sup>17</sup>, Eduard Vieta<sup>6</sup>, Birgit Völm<sup>19</sup>, Charlotte Wilson-Jones<sup>2</sup> and Laura Woods<sup>20</sup>**

<sup>1</sup>Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College, London, UK; <sup>2</sup>Maudsley Hospital, South London & Maudsley NHS Foundation Trust, London, UK; <sup>3</sup>The Centre for Psychiatry, Imperial College London, London, UK; <sup>4</sup>Wotton Lawn Hospital, 2gether NHS Foundation Trust, Gloucester, UK; <sup>5</sup>National Association of Psychiatric Intensive Care Units, East Kilbride, Glasgow, UK; <sup>6</sup>Hospital Clinic, Institute of Neurosciences, University of Barcelona, Barcelona, Catalonia, Spain; <sup>7</sup>Mill View Hospital, Sussex Partnership NHS Foundation Trust, Hove, East Sussex, UK; <sup>8</sup>Department of Psychiatry, Social Psychiatry & Psychotherapy, Hannover Medical School, Hanover, Germany; <sup>9</sup>Central North West London NHS Foundation Trust, London, UK; <sup>10</sup>Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK; <sup>11</sup>Northumberland, Tyne & Wear NHS Foundation Trust, Newcastle upon Tyne, UK; <sup>12</sup>South West London & St George's Mental Health NHS Foundation Trust, London, UK; <sup>13</sup>St George's, University of London, London, UK; <sup>14</sup>Central & North West London NHS Foundation Trust, London, UK; <sup>15</sup>CALM Training Ltd, Menstrie, UK; <sup>16</sup>Oxleas NHS Foundation Trust, Dartford, UK; <sup>17</sup>South London & Maudsley NHS Foundation Trust, London, UK; <sup>18</sup>Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; <sup>19</sup>Institute of Mental Health, School of Medicine, University of Nottingham, Nottingham, UK; <sup>20</sup>The Hellingly Centre, Forensic Health Care Services, Sussex Partnership NHS Foundation Trust, East Sussex, UK

\*Joint first author (both first authors contributed equally to the article)

Correspondence to: Faisil N Sethi, Maudsley Hospital, South London & Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK; [faisil.sethi@slam.nhs.uk](mailto:faisil.sethi@slam.nhs.uk)  
Maxine X Patel, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, Box 68, 16 De Crespigny Park, London SE5 8AF, London, UK; [maxine.patel@kcl.ac.uk](mailto:maxine.patel@kcl.ac.uk)

The British Association for Psychopharmacology and the National Association of Psychiatric Intensive Care and Low Secure Units developed this joint evidence-based consensus guideline for the clinical management of acute disturbance. It includes recommendations for clinical practice and an algorithm to guide treatment by healthcare professionals with various options outlined according to their route of administration and category of evidence. Fundamental overarching principles

are included and highlight the importance of treating the underlying disorder. There is a focus on three key interventions: de-escalation, pharmacological interventions pre-rapid tranquillisation and rapid tranquillisation (intramuscular and intravenous). Most of the evidence reviewed relates to emergency psychiatric care or acute psychiatric adult inpatient care, although we also sought evidence relevant to other common clinical settings including the general acute hospital and forensic psychiatry. We conclude that the variety of options available for the management of acute disturbance goes beyond the standard choices of lorazepam, haloperidol and promethazine and includes oral-inhaled loxapine, buccal midazolam, as well as a number of oral antipsychotics in addition to parenteral options of intramuscular aripiprazole, intramuscular droperidol and intramuscular olanzapine. Intravenous options, for settings where resuscitation equipment and trained staff are available to manage medical emergencies, are also included.

**Key words:** acute disturbance; violence; aggression; rapid tranquillisation; de-escalation; antipsychotics; benzodiazepines; psychiatric illness

## Introduction

### *Acute disturbance*

This guideline covers the clinical management of ‘acute disturbance’, which we use here as a composite term to include the concepts of ‘agitation’, ‘aggression’ and ‘violence’ in the context of an acute mental state associated with an underlying mental and/or physical disorder. No commonly accepted definitions exist for any of these concepts.

Definitions of agitation from the scientific literature regularly cited in guidance documents have tended to be restricted to the field of dementia. One of the most commonly used definitions was proposed by Cohen-Mansfield (1986) who defined agitation in those with cognitive impairment or dementia as ‘inappropriate verbal, vocal or motor activity that is not explained by needs or confusion per se’ (NICE, 2015a; Seitz et al., 2011). The Agitation Definition Working Group of the International Psychogeriatric Association described agitation in the context of dementia as ‘exhibiting behaviour consistent with emotional distress ... manifesting excessive motor activity, verbal aggression, or physical aggression, and ... evidencing behaviours that cause excess disability and are not solely attributable to another disorder’ (Cummings et al., 2015). National Institute for Health and Care Excellence (NICE) guidelines on conditions other than dementia have not used published definitions of agitation, although NG10 does identify agitation as one of the ‘symptoms or feelings that may lead to violence and aggression’ (NICE, 2015b). It recognises agitation as part of an ‘escalating behaviour pattern, starting with restlessness, moving through agitation and irritability, through verbal aggression ... and culminating in an assault’.

The terms aggression and violence are often used inter-

changeably and NICE Guideline NG10 does not clearly differentiate between the two terms, stating that ‘violence and aggression refer to a range of behaviours or actions that can result in harm, hurt or injury to another person, regardless of whether the violence and aggression is behaviourally or verbally expressed, physical harm is sustained or the intention is clear’ (NICE, 2015b). Alternatively, a widely accepted definition of violence by the World Health Organization (2014) is the ‘intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation’. The World Health Organization definition excludes damage to property and also requires intent, which might be problematic in the context of acutely mentally unwell individuals and therefore does not seem entirely appropriate for the purposes of this guideline. Some use the term aggression to denote a state that is less severe than violence, whereas others use it to describe behaviours such as damage to property rather than against the person (Yudofsky et al., 1986).

Thus, we define ‘acute disturbance’ as an acute mental state associated with an underlying mental and/or physical disorder in the form of: (i) agitation and distress, which is excessive verbal or motor activity that may or may not lead to aggression or violence; or (ii) actual aggression or violence entailing harm, hurt or injury to another person, or damage to property regardless of whether it is verbally or behaviourally expressed, physical harm is sustained, or the intention is clear.

### *De-escalation and rapid tranquillisation*

In this guideline, we define ‘de-escalation’ as an explicitly collaborative process involving a range of verbal and non-

verbal interventions that aim to reduce agitation and distress, with the purpose of averting aggression or violence. This differs slightly from the definition of de-escalation given by the NICE Guideline NG10 (NICE, 2015b), in that our definition explicitly focuses on non-verbal, as well as verbal interventions.

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 difference being whether only parenteral formulations of medication are considered to constitute RT or if oral formulations are also included. NICE (2015b) concentrates solely on the parenteral route and the aim of achieving sedation, and so defines RT as ‘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 required’. This differs from the earlier definition in the NICE (2005) guideline, which explicitly included oral formulations too. For clarity, the definition of RT in our guideline will be parenteral pharmacological intervention, in keeping with the NICE (2015b) guideline.

If oral medication is administered, this may be the only pharmacological intervention, although in some cases RT will be administered subsequently, and so we will refer to this time period as ‘pre-RT’. The aim of offering oral medication to agitated patients is to pre-emptively address acute disturbance and to avoid escalation and the need for parenteral medication and physical restraint. Oral medication administered in the context of the clinical management of acute disturbance will often be an ‘as required’ or *pro re nata* (PRN) prescription, given at the discretion of nursing staff, when deemed necessary. Arguably, this can lead to patients receiving unnecessary medication (Curtis and Capp, 2003). However, it is common practice for PRN medication to be administered to patients admitted to acute psychiatric wards for acute disturbance. This practice is based on clinical experience rather than evidence as there are no published randomised controlled trials (RCTs) comparing the efficacy of PRN medication with regular medication for the treatment of psychotic symptoms or acute disturbance (Douglas-Hall and Whicher, 2015). It should also be highlighted that the prescribing of antipsychotics PRN can lead to polypharmacy and high cumulative doses of antipsychotics, for which there is also no evidence of increased effectiveness over standard doses for the management of acute disturbance (Paton et al., 2008; Royal College of Psychiatrists, 2014). This practice also carries an enhanced burden of adverse effects and

associated monitoring requirements. The same is true for benzodiazepines. Nonetheless, PRN medication can also play an important part of the clinical management of acute disturbance to reduce the risk of incidents.

Formulation and route of administration are also of particular importance for pre-RT and RT medication. Some medications are available in more than one formulation and not all of them are individually examined in the available literature. The pharmacokinetics of different formulations of the same drug can vary markedly; this critically includes time to peak plasma concentration (T<sub>max</sub>), which is a useful but crude gauge for time to onset of action of effect (usually some level of sedation). There is a complex interplay between absorption, T<sub>max</sub>, time to onset of action of effect, duration of desired effect, half-life and risk of acute side effects (NPSA, 2007). In general, oral tablets, capsules and liquids are absorbed via the gastrointestinal tract and have the longest T<sub>max</sub>. All orally administered medicines are absorbed into the bloodstream and pass through the liver before entering the systemic circulation. Where that medicine is metabolised by the liver, this ‘first-pass’ effect results in a lower proportion of an oral formulation being available in the systemic circulation than if the same medication is administered by the intramuscular (IM) or intravenous (IV) route. The magnitude of any first-pass effect is medication specific but for some medications this will mean that lower parenteral doses than oral doses are effective. When a medicine is administered by the IM route, T<sub>max</sub> is generally reached more rapidly compared with oral administration; this can be helpful when time to onset of action is important. Adherence to medication can be enhanced by using orodispersible tablets designed to dissolve on contact with saliva or water. Buccal, sublingual and oral-inhaled absorption have similar or shorter T<sub>max</sub> when compared with IM formulations. The fastest time to peak plasma levels, and hence the shortest time to T<sub>max</sub>, is for IV medications. Thus, IV administration leads to a more immediate onset of action than for IM and is more predictable and easier to titrate.

#### *Restraint and restrictive practices*

In clinical practice, RT tends to be associated with the use of restraint and restriction. Manual restraint is defined by NICE (2015b) as ‘a skilled, hands-on method of physical restraint used by trained healthcare professionals to prevent patients from harming themselves, endangering others or compromising the therapeutic environment. Its purpose is to safely immobilise the patients’. In our guideline, we will use the term physical restraint instead of manual restraint; the former being the more commonly used term in the United Kingdom (UK). Physical restraint can occur without the use of RT and vice versa. A patient, once physically restrained, may agree to take oral medication.

In general, however, for a patient to receive RT safely, some degree of physical restraint is required.

Physical restraint should be distinguished from mechanical restraint, the latter being very rarely used in the UK. Mechanical restraint is defined as ‘a form of restrictive intervention that refers to the use of a device (e.g. belt or cuff) to prevent, restrict or subdue movement of a person’s body, or part of the body, for the primary purpose of behavioural control’ (Department of Health, 2015). It is used in response to behaviour, that poses significant risk to the individual or others of serious long-term harm or immediate injury, and involves the use of some sort of equipment. The Care Quality Commission (2014) recognised that the use of mechanical restraint may be considered as the least restrictive intervention in some rare and specific cases and may present less risk to the individual than the alternative of prolonged physical restraint or transfer to a more restrictive setting.

Seclusion is defined in the Mental Health Act Code of Practice as ‘the supervised confinement and isolation of a patient, away from other patients, in an area from which the patient is prevented from leaving, where it is of immediate necessity for the purpose of the containment of severe behavioural disturbance which is likely to cause harm to others’ (Department of Health, 2015). Seclusion is different from voluntary temporary segregation (sometimes mistakenly referred to as ‘time out’), when a patient agrees to spend time in an area away from others, with no restrictions on returning to contact with other patients (Department of Health, 2015). Some mental health services have a designated ‘extra care area’, which may be an alternative to seclusion; a closely supervised space where a patient may be nursed away from other patients (NAPICU, 2016). Seclusion should only be used when other measures for managing violence have failed. RT may be required at the same time. This can be especially challenging when considering safe monitoring following RT.

There is a drive internationally to reduce restrictive practices. In the UK, there is a government directive to reduce all forms of restrictive practices, with an objective of ending the use of prone (face-down) restraint; restrictive practices should only be used as a last resort in emergency situations (Department of Health, 2014). There is also a focus on corporate responsibility; each Trust Board should be fully informed of the position of their Trust on restrictive practices and the management plan to reduce their use, should identify an executive director to lead on recovery approaches and reducing restrictive practices, and should publish an annual report on its use of restrictive interventions (Mental Health Network, 2014).

Low-level evidence regarding interventions to reduce seclusion includes the following: increased monitoring and regulation, leadership changes, staff training and

changes, improved staff to patient ratios, treatment plan improvements and even aromatherapy (Gaskin et al., 2007). Recently, one study found that the introduction of body cameras for staff has led to a reduction in untoward incidents (Hardy et al., 2017).

Training is important when trying to reduce restrictive practices. Recognising the early signs of agitation is crucial, with the aim of reducing further restrictive interventions, and staff should be trained in the use of techniques aimed at defusing anger. NICE (2015b) recommends that all staff receive training in de-escalation, although we note that a systematic review of 38 observational studies concluded that overall the quality of evidence was low and the findings were inconsistent, so the positive effects from training staff in de-escalation techniques could not be confirmed (Price et al., 2015). A large number of companies also offer prevention and management of violence and aggression (PMVA) training programmes (Bowers et al., 2006) as well as ‘breakaway’ training sessions to help staff to escape when they are being physically attacked. As yet, there are no nationally agreed recommendations regarding how and when such techniques should be used, and the effectiveness of the training approaches currently offered is largely unsupported by evidence (McKenna and Paterson, 2006).

#### *Rapid tranquillisation practice in the UK*

In 2016, the Prescribing Observatory for Mental Health (POMH-UK; Barnes and Paton, 2011) initiated a quality improvement programme in mental health services addressing RT in the context of the pharmacological management of acute disturbance (POMH-UK, 2017). A total of 58 specialist mental health Trusts or healthcare organisations participated in the baseline clinical audit and submitted data on 2172 episodes of acute disturbance in patients on acute adult ( $n = 1455$ ), psychiatric intensive care ( $n = 444$ ) or low, medium or high secure wards ( $n = 273$ ) (POMH-UK, 2017). Being the largest audit of such practice, the data provide a useful insight into the clinical management of acute disturbance in mental health services in the UK. In the vast majority of episodes ( $n = 2061$ ; 95%), one or more non-pharmacological interventions were employed. Predominantly, these were de-escalation strategies (verbal de-escalation and/or distraction and/or removal of precipitating factors), control and restraint, or observation. Control and restraint was approximately three times more likely to be used in association with parenteral medication, as compared with oral medication (POMH-UK, 2017).

For these episodes of acute disturbance, oral medication only was administered in half ( $n = 1091$ ; 50%). Parenteral (IM and/or IV) medication only was given in 43% of episodes ( $n = 936$ ); this was almost all administered IM, the use of IV medication being limited to only two instances



of IV haloperidol usage. A combination of oral and IM/IV medication was given in 145 (7%) of episodes. In over four-fifths of episodes ( $n = 1756$ ; 81%), the patient was already prescribed regular antipsychotic medication and for 5% this was high dose. The administration of additional antipsychotic medication for acute disturbance tipped the total daily dosage over the high-dose threshold for patients in a further 13% of episodes (POMH-UK, 2017).

Of the episodes of acute disturbance for which an oral medication was used, this was most commonly an oral benzodiazepine alone ( $n = 726$ ; 59%). An oral benzodiazepine was also used in combination with oral antipsychotic medication in 15% of episodes and with oral promethazine in a further 5%. The choice of oral benzodiazepine was lorazepam in over 90% of cases, with a median dose of 1 mg. In addition to its use in combination with an oral benzodiazepine, oral antipsychotic medication was used on its own in 12% of such episodes and with oral promethazine in 2%. Haloperidol was by far the most commonly used oral antipsychotic medication, in nearly three-quarters (72%) of cases, with a median dose of 5 mg (POMH-UK, 2017).

An IM benzodiazepine was administered in two-thirds (67%) of episodes where parenteral medication was used and in over a third of instances (39%) was the only IM medication. Lorazepam was almost invariably the IM benzodiazepine used (99% of instances), with a median dose of 2 mg. An IM antipsychotic medication was used in half (50%) of such episodes and for around a fifth of episodes (18%) was the only IM medication used. IM haloperidol was the antipsychotic most commonly prescribed (67%), with a median dose of 5 mg. Other IM antipsychotics used were IM aripiprazole (14%), IM olanzapine (9%), IM promazine (1%) and IM levomepromazine (1%). IM promethazine alone was administered in 74 (7%) of episodes (POMH-UK, 2017).

Combinations of IM medications were used in 381 episodes, including 295 cases with IM benzodiazepine plus IM antipsychotic. The most common combination was IM lorazepam plus IM haloperidol. The combination of IM promethazine plus IM antipsychotic ( $n = 44$ ; 4%) was used relatively infrequently, despite being the recommended combination in the NICE Guideline NG10 (NICE, 2015b). The combination of IM benzodiazepine plus IM promethazine ( $n = 42$ ; 4%) was used almost as frequently as IM promethazine plus IM antipsychotic. It also suggests that around one quarter of patients did not respond to RT (POMH-UK, 2017).

Nationally, there is evidence of poor adherence to physical health monitoring recommendations. The POMH-UK audit found that there was no documented physical health monitoring in the hour after RT in 42% ( $n = 450$ ) of episodes and in 45% ( $n = 201$ ) of these episodes no line-of-sight psychiatric observations were recorded

either. Thus, in almost 20% of the episodes recorded nationally there was no documented monitoring (physical health or psychiatric) in the hour following RT (POMH-UK, 2017).

### *National guidelines*

In the UK, the most prominent current clinical guideline on RT is entitled *Violence and aggression: Short-term management in mental health, health and community settings* (NG10, NICE, 2015b). This was an update of a previous guideline (CG25) published in 2005 (NICE, 2005). NICE also published an additional guideline (NG11) on prevention and intervention for challenging behaviour presented by people with learning disabilities (NICE, 2015c). RT is mentioned in current NICE guidelines for psychosis and schizophrenia (NICE, 2014a), bipolar disorder (NICE, 2014b) and dementia (NICE, 2006), all of which point to CG25 for detailed recommendations, as they were published prior to NG10. NICE antenatal and postnatal mental health guidelines provide additional specific recommendations for RT in pregnancy (NICE, 2014c). In addition to these guidelines, which provide comprehensive clinical recommendations, NICE has also reviewed specific medications used in RT including IM promethazine (NICE, 2014d) and inhaled loxapine (NICE, 2013). This information is subsumed within NG10.

NG10 refers to the use of pharmacotherapy in three specific situations: (i) in an individualised management package to decrease the risk of violence or aggression; (ii) as required (PRN) medication as part of a strategy to de-escalate or prevent situations that may lead to violence and aggression; and (iii) in the context of RT. This is a useful basic framework when drawing up treatment plans. NICE recommendations also include developing a multidisciplinary strategy targeting specific symptoms as soon as a patient at risk of violence or aggression is admitted to an inpatient unit, which should then be reviewed at least weekly. If RT is being used, it is recommended that a senior doctor reviews the medication regimen at least daily. There should be clarity about the rationale and circumstances for PRN medication with maximum daily doses specified that should ordinarily not exceed British National Formulary (BNF) (Joint Formulary Committee, 2017) limits except under the direction of a senior doctor.

In terms of drug choice for RT, NICE recommends either IM lorazepam alone or IM haloperidol plus IM promethazine for RT in adults, taking the following factors into account: the patient's preferences or advance statements and decisions; pre-existing physical health problems or pregnancy; possible intoxication; previous response to these medications, including adverse effects; potential for interactions with other medications; and the total daily

dose of medications prescribed and administered. IM lorazepam is preferred if there is limited clinical information available, if the patient has not been prescribed antipsychotic medication before, if there is evidence of cardiovascular disease including a prolonged corrected QT interval (QTc), or if no electrocardiogram (ECG) has been carried out (NICE, 2015b). If there is a partial response to IM lorazepam, a further dose is recommended. However, if there is no response, IM haloperidol plus IM promethazine is recommended for consideration. Similarly, if there is a partial response to IM haloperidol plus IM promethazine a further dose is suggested, but if there is no response, IM lorazepam is recommended if it has not already been used. If it has, then a review and possible second opinion is suggested.

In the UK, NICE guidelines are complemented by those produced by the British Association for Psychopharmacology (BAP). Those relating to, for example, schizophrenia (Barnes et al., 2011) and bipolar disorder (Goodwin et al., 2016) provide additional recommendations regarding the generic treatment of these conditions, which will contribute to an overall decrease in risk of acute disturbance. However, with the exception of the BAP perinatal guidelines (McAllister-Williams et al., 2017) there are no specific recommendations made with regards to RT.

Other documents that are relevant to prescribers managing acute disturbance include the Royal College of Psychiatrists consensus statement on the use of high-dose antipsychotic medication (Royal College of Psychiatrists, 2014), recommendations on the use of licensed medication in unlicensed situations (Royal College of Psychiatrists Psychopharmacology Committee, 2017), and prescribing guidance for unlicensed medicines by the General Medical Council (GMC, 2013).

### *International perspectives*

The most recent comprehensive review of the evidence base for the management of acute disturbance is a consensus document produced by the World Federation of Societies for Biological Psychiatry (WFSBP) (Garriga et al., 2016). The guideline was developed after a systematic review, and a consensus exercise of 24 international experts from different countries based on the Delphi method.

Their recommendations emphasised that proper assessment of acute disturbance includes ruling out any possible medical cause as a first step. The differential diagnosis process should include not only a review of the medical and psychiatric history, but also a timely reconstruction of the episode of acute disturbance, physical, neurological and mental examination as well as a minimum set of complementary explorations (vital signs, capillary glucose, oxygen saturation and urine toxicology test). Verbal de-escalation is recommended before pharmacological

intervention together with environmental modifications and a focus on strategies to enhance engagement with the patient during all aspects of the clinical management process. Physical restraint should be considered a last-resort strategy. For pharmacological treatment, the WFSBP guidelines suggest the patient should be involved as much as possible in the selection of the medication.

Pharmacological treatments should match the underlying condition and, if no specific diagnosis is achieved, acute disturbance should be considered to emerge from a medical cause. In acute disturbance due to a medical condition or alcohol intoxication, the WFSBP guidelines suggest that antipsychotics should be preferred over benzodiazepines. If acute disturbance is due to alcohol withdrawal, then the use of benzodiazepines over antipsychotics is advised. If a psychiatric disorder is causing the acute disturbance, antipsychotic medication is recommended for psychotic agitation whereas benzodiazepines should be considered for non-psychotic agitation. The route of medication administration will depend on the severity of the scenario and the degree of patient cooperation, prioritising non-invasive formulations (oral or inhaled) over IM/IV routes. It advises attempts to achieve monotherapy, avoiding medication combinations where possible. Medication adjustment for renal and/or hepatic impairment as well as in the elderly has to be considered (Garriga et al., 2016).

Guidelines highlight a need to increase critical discussion on effective interventions in the management of acute disturbance and in recent years the literature has expanded. This includes the early consensus work of Allen et al. (2001, 2005) as well as relevant reports by: the American Association for Emergency Psychiatry (Holloman and Zeller, 2012) with Project BETA; the American College of Emergency Physicians (Lukens et al., 2006); and the Joint Commission on Accreditation of Healthcare Organizations and the Centres for Medicare and Medicaid (The Joint Commission, 2000). The current WFSBP guidelines (Garriga et al., 2016) were preceded by agitation guidance sections in other documents related to the management of schizophrenia and mania (Grunze et al., 2010; Hasan et al., 2012). Other European societies have also created guidelines, including the Austrian Society for Neuropsychopharmacology and Biological Psychiatry (Kasper et al., 2013; Frey et al., 2015).

### *A patient's perspective*

The following excerpt was provided by a member of the consensus group who has lived experience of acute inpatient clinical settings and is the patient representative on the Executive Committee of the National Association of Psychiatric Intensive Care Units.

Patients so acutely disturbed to be considered for RT are extremely fearful of almost anything they cannot easily

understand. All comparisons are likely iniquitous; trust in almost everything is virtually impossible. Worse still, if such fragility of trust is dashed, this can lead to aggression, or even violence. This emphasises the importance that RT should only be used when severe disturbance, aggression or violence is deemed to be imminent. Within this context, we consider how we might most effectively bring about a calmer state avoiding further harm to the patient, others or objects.

To be rapid, the efficacy of tranquillisation is fostered by the route of least ambiguity, measured by the willingness of both the patient and clinician to engage. Deviation from a clear simple approach may have the effect of loading years to the process of recovery. Consequently, listening and careful observation of the patient and environment are advised as this may yield clues to what triggered the heightened anxiety. Recent change of people or objects may be exacerbating factors and addressing these may help calm the patient. Extreme care in introducing no more anomalies is advised. Ideally, changes should be explained by whoever is considered most trusted and a single communicator will reduce confusion. However stressful the situation becomes, clinicians should be easily identifiable, well trained and presenting positively and confidently in their actions as lack of confidence will exacerbate the anxiety of the patient.

Further, only medicines and routes of administration that clinicians are confident and sure of should be used. Lack of confidence can reduce effectiveness. Communication with the patient as soon as is sensible is key and should include an explanation of the procedure they have been through and why, with great care given to instil feelings of hope. Carefully tailored reward for patient participation towards manageable and sustainable goals can be considered. Post-treatment sharing of both patient and clinician experience is essential to evolve improved specific and general protocols. Clinicians from all disciplines across all health services should share common practices (Allen et al., 2003; NICE, 2012) as this will result in fewer patient presentations through greater understanding.

#### *Guideline scope*

The BAP has published a series of evidence-based guidelines for the use of drugs in patients with psychiatric disorders with an emphasis on producing comprehensive, concise and useable guidance based on a review of the relevant evidence (see <https://www.bap.org.uk>). The National Association of Psychiatric Intensive Care and Low Secure Units (NAPICU) has a long history of promoting best multidisciplinary practice in clinical services that manage acute disturbance and challenging behaviour in mental disorders (see <http://www.napicu.org.uk>). The goal of this joint BAP–NAPICU guideline is to provide recom-

mendations for healthcare professionals in the use of de-escalation methods and psychotropic medication for the clinical management of acute disturbance. Most of the evidence reviewed here relates to emergency psychiatric care or acute psychiatric inpatient care, although we also sought evidence relevant to other common clinical settings including the general acute hospital and forensic psychiatry. These guidelines are designed to be complementary to previous guidelines and reports. For example, the most recent NICE guidelines reviewed RCT evidence for the use of medications for acute disturbance, although they placed relatively less emphasis on the use of oral formulations of medication (NICE, 2015b).

At the outset it was decided that we would not attempt to carry out a comprehensive review of evidence for the management of acute disturbance relating to children and young people, those with a learning disability or traumatic brain injury, or older adults with or without dementia. Although these are important topics, the paucity of good evidence relating to these groups would make it impossible to write similarly evidence-based recommendations. Further, we have not reviewed the numerous clinical rating scales for measuring the degree or frequency of acute disturbance and the outcomes of management approaches (for a recent review see Garriga et al., 2016). Staffing, cultural influences and judicial settings are also not considered. The use of seclusion as an intervention, as well as physical and mechanical restraint measures and techniques are briefly described above, but we have not reviewed them extensively and make no recommendations.

## **Method**

A group of experts was invited to an initial meeting in June 2017 organised jointly by the BAP and NAPICU. Expert participants were asked to review key areas and highlight recent data from systematic reviews, RCTs or observational studies. After each brief presentation, a discussion of the important issues identified areas of agreement or uncertainty. A literature review was then conducted to compile the evidence for the key areas on which the consensus points had been based. This review, together with proposed recommendations and their evidence grading, was circulated to members of the consensus group and discussed in January 2018 at a second smaller meeting of the experts. Their feedback was, as far as possible, incorporated into the final version of these guidelines.

The guideline recommendations are linked to relevant evidence through the literature review. However, our methodology and available funding did not allow for a systematic review of all possible data from primary sources. Existing systematic reviews, RCTs and observational studies were identified from PubMed, Medline and EMBASE and from the Cochrane Database. Published NICE guidelines on



Table 1. **Categories of evidence and strength of recommendations****Categories of evidence for causal relationships and treatment**

- Ia: Evidence from meta-analysis of randomised controlled trials  
 Ib: Evidence from at least one randomised controlled trial  
 IIa: Evidence from at least one controlled study without randomisation  
 IIb: Evidence from at least one other type of quasi-experimental study  
 III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies  
 IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

**Strength of recommendation**

- A: Directly based on category I evidence from meta-analysis of randomised controlled trials, at least one large, good quality, randomised controlled trial or replicated, smaller, randomised controlled trials  
 B: Directly based on category II evidence from meta-analysis of randomised controlled trials, at least one large, good quality, randomised controlled trial or replicated, smaller, randomised controlled trials, or extrapolated a recommendation from category I evidence  
 C: Directly based on category III evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies, or extrapolated recommendation from category I or II evidence  
 D: Directly based on category IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities, or extrapolated<sup>a</sup> recommendation from category I, II or III evidence  
 S: Standard of good practice

<sup>a</sup>Extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.

RT (CG25, NICE, 2005; NG10, NICE, 2015b; and Quality Standard QS154, NICE, 2017) were also considered.

The categories of evidence applied to the literature reviewed and the strength of the recommendations made are described in Table 1, which is derived from work by Shekelle et al. (1999) on the development of clinical guidelines. RCTs must have an appropriate control treatment arm. For primary efficacy this should include a placebo condition, although for psychological interventions this may not be feasible. 'Strength of recommendation' is rated A to D according to category of evidence. A lower rating implies a less extensive or robust body of evidence but not necessarily lesser clinical importance. The S category represents a standard of care, which describes a consensus based on good practice standards rather than evidence. In the guideline, the recommendations are grouped altogether (see Recommendations for interventions), rather than at the end of each section of evidence reviewed to enable the reader to see the foundations, upon which the algorithm is based, all in one place.

There are a number of factors that should be considered when deriving recommendations for practice from the existing evidence base:

- For RCTs of RT, trials vary in design and most have a relatively small sample size. Further it is challenging to design trials to demonstrate whether pre-emptive use of oral medication pre-RT leads to reduced need for parenteral RT.
- Primary outcome measures are multiple, diverse and measured at different pre-set time points. Further, they commonly include achieving sedation or the state of falling asleep or time to desirable state. The proportions of participants who become calm are not consistently reported.
- With respect to 'onset of action', the populations treated in clinical trials are very different. Onset of

sedation and tranquillisation is often reported in trials but how that relates to treatment of acute disturbance is not defined.

- RCTs of RT conducted in other countries with different healthcare systems or in different healthcare settings may or may not be generalisable to the UK setting. Similarly, RCTs conducted in acute hospital settings are not necessarily generalisable to psychiatric settings as in the former there is ready access to both anaesthetists and the equipment required to deal with medical emergencies caused by over-sedation.
- Ethical considerations, particularly the requirement that participants in research studies give informed consent, make it difficult to conduct RCTs of RT; this is particularly true in UK settings.
- Patients who are able and willing to give informed consent to participate in such RCTs are less behaviourally disturbed than those who receive RT in routine clinical practice. Thus, the findings of such studies may not be directly extrapolated to more severely disturbed patients for whom clinicians are likely to use tried and tested methods to defuse high-risk
- Trials evaluating the use of an antipsychotic in RT, as compared with placebo, recruit participants who are not already receiving regular antipsychotic medication. Consequently, treatment with a single antipsychotic is confirmed as reducing acute disturbance more effectively than placebo, but the common clinical practice of adding a second PRN antipsychotic to manage acute disturbance, for a patient already prescribed one antipsychotic regularly, is untested in clinical trials.
- In clinical practice, the initial attempt at RT fails to achieve sedation or a state of calmness in a significant minority of participants. In such cases, there is very limited evidence on which to base recommendations for further interventions.

## De-escalation

De-escalation is commonly practised in many mental health settings. One study of English acute inpatient services showed that over half (53%) of the patients were subject to de-escalation in the first two weeks of their admission (Lavelle et al., 2016). De-escalation is described as potentially useful in averting the need for physical restraint and it is suggested that de-escalation should generally precede and accompany the use of RT or seclusion (NICE, 2015b). De-escalation can also involve the use of purpose-designed de-escalation rooms or temporary separation from other patients (Royal College of Nursing, 2016).

De-escalation can be considered as a process with discrete phases and identifiable components. Various articles have described theoretical models of de-escalation as involving a series of stages either as a linear process (Bowers, 2014; Paterson et al., 1997) or a circular process (Dix and Page, 2008). The linear model of Bowers (2014) comprised delimiting (establishing safety), clarifying (identification of the patient perspective or need) and resolving (negotiation) to reach a mutual solution. This has some parallels with research in a Danish mental health setting based on staff interviews, where the first phase was described as involving creating a 'safe place' including managing physical distance and environment, and the second phase was establishing mutual relations with empathy, which then underpins the phase of collaborative problem solving (Berring et al., 2016).

Gaynes et al. (2016) conducted a systematic review of the literature examining strategies for preventing aggressive behaviour. Broad criteria allowed inclusion of studies of non-pharmacological interventions and articles included: risk assessment, multimodal programmes, environmental or group psychotherapeutic interventions and medication protocols. From 1983 papers of initial interest, 17 RCTs met their inclusion criteria; of these, only one RCT incorporated de-escalation but was not described in detail. This RCT evaluated the introduction of 'six core strategies' in a multimodal intervention in a Finnish high-security service for men. Patient-days with seclusion, restraint or room observation reduced from 30% to 15% for intervention wards versus from 25% to 19% for control wards conducting treatment as usual ( $p < 0.001$ ). Recorded violent incidents reduced from 1.1% to 0.4% for the intervention wards and from 0.1% to 0% for control wards (Putkonen et al., 2013).

In the UK, the Safewards Model was evaluated in a cluster RCT of 31 adult acute wards. This model highlighted aspects of working in wards that are considered to identify potential 'flashpoints' and described 10 interventions, each of which were designed to contribute to a decrease in conflict or improve management such that the need for containment is reduced. The RCT reported that

staff can successfully intervene to manage flashpoints to significantly reduce conflict incidents (14.6% decrease; 95% confidence interval, CI, 5.4–23.5%;  $p = 0.004$ ) and the use of physical restraint, seclusion and RT (23.6% decrease; 95% CI 5.8–35.2%;  $p = 0.001$ ) (Bowers et al., 2015). One of the interventions was a specific de-escalation element (Bowers 2014) but this was not evaluated individually and thus the degree of contribution to the overall results obtained is difficult to determine. A large Australian pre-/post-design study involving 18 wards failed to replicate these results; this study found no reduction in restrictive practices including seclusion ( $p = 0.76$ ; Hamilton et al., 2016).

In a non-systematic review of the qualitative literature on de-escalation, 11 of 94 articles were selected for inclusion from which de-escalation components were identified (Price and Baker, 2012). The need to 'behave empathically and respectfully' was highlighted and a number of key themes were identified including: staff skills and characteristics of successful de-escalators; maintaining personal control; verbal/nonverbal skills; and de-escalation context. Collaborative problem-solving and compassionate non-confrontational limit setting were also identified as options (Price and Baker, 2012). Kuivalainen et al. (2017) conducted a qualitative analysis and found that 27% of 133 incident forms for de-escalation in a forensic setting identified some method of environmental management.

Price et al. (2018) conducted semi-structured interviews with inpatient ward staff, including three psychiatric intensive care units in the UK. Their findings suggested that staff differentiated between 'non-physical control techniques' and 'support techniques', the latter representing discrete de-escalation skills and encompassing reframing, problem identification and solving, distraction, reassurance and passive intervention. They highlighted the significance of assessment but also the role of trial and error in attempting to establish which combination of techniques may work best. Similarly, a questionnaire-based survey of nursing staff ( $n = 72$ ) investigated the nature of de-escalation in secure mental health settings and identified a series of key skills including expressing empathy, care, humour and using distraction and calmness (Hallett and Dickens, 2015). Further components included displaying self-control to present in a calm manner, managing the environment (including use of other staff and use of separation) and careful attention to ensure the dignity of the patient was not compromised (Hallett and Dickens, 2017). Providing soothing activities may facilitate emotional regulation (Champagne and Stromberg, 2004). The use of humour may seem intuitively inappropriate in a context in which aggression is imminent and distress evident, but careful and respectful usage may change the patient's emotional

**Table 2.** De-escalation components

Component	Description	Highest level of evidence	Other relevant citations
Continual risk assessment	Dynamic cycles of micro-assessment are required. These entail continually monitoring the nature/degree of risk including responses to staff efforts.	Hallet and Dickens (2015): qualitative study surveying medium secure unit staff ( $n = 72$ ); six core themes identified	Dix and Page (2008); Price and Baker (2012); NICE (2015b)
Self-control techniques	Exposure to aggression can have an impact on staff emotional regulation, which needs to be actively and consciously managed.	NICE (2015b): national guideline	Bowers (2014); Paterson and Leadbetter (1999); Richter (2006)
Avoidance of provocation	Understanding and seeking to avoid known triggers or otherwise behaving in a way likely to provoke aggression.	Richmond et al. (2012): consensus statement at a national level	NICE (2015b); Richter (2006)
Respect patient space	Staff should actively increase the personal space they afford the patient to decrease any perceived threat.	NICE (2015b): national guideline	Berring et al. (2016); Paterson and Leadbetter (1999); Richmond et al. (2012); Turnbull et al. (1990)
Management of environment	Moving other patients away or suggesting to the patient that the location of interaction is moved to another room or offering a choice of preferred activity that the patient finds soothing can modify the level of stimulation.	Kuivalainen et al. (2017): qualitative analysis of incident forms ( $n = 133$ ) in a forensic setting; thematic analysis identified this component in 27% of incidents	Bowers (2014); Hallet and Dickens (2015); NICE (2015b); Paterson and Leadbetter (1999); Price and Baker (2012)
Passive intervention and watchful waiting	Consciously minimising the cognitive load of the patient who may be struggling to sustain emotional regulation whilst actively assessing the situation.	Price et al. (2018): qualitative interviews ( $n = 20$ ) with staff from five acute services; thematic analysis identified six sub-themes, including this component	Lowry et al. (2016); NICE (2015b)
Empathy	Display empathy verbally and non-verbally. Appearing calm is helpful, but an acknowledgment of the patient's distress via mirroring can be helpful.	NICE (2015b): national guideline	Berring et al. (2016); Bowers (2014); Richter (2006); Turnbull et al. (1990)
Reassurance	Fear or shame may underlie overt aggression. Reassuring the patient that they are safe, respected, valued and that nobody will harm them, can be critical.	Hallet and Dickens (2015): qualitative study surveying medium secure unit staff ( $n = 72$ ); six core themes identified; this component was a sub-theme of communication	Berring et al. (2016); Nau et al. (2009); Price et al. (2018)
Respect and avoidance of shame	Shame may trigger aggression in patients and staff. Seeking solutions that allow the patient to retain their dignity is important.	Berring et al. (2016): multiple qualitative case studies ( $n = 42$ ) across a variety of clinical settings; this component was repeatedly identified	Bowers (2014); Lavelle et al. (2016); NICE (2015b); Price and Baker (2012); Richmond et al. (2012); Richter (2006)
Appropriate use of humour	Changing the emotional dynamic of a situation underpins de-escalation and the appropriate but importantly empathic use of humour may do this.	Hallet and Dickens (2015): qualitative study surveying medium secure unit staff ( $n = 72$ ); six core themes identified; this component was a sub-theme of interpersonal skills	Berring et al. (2016); Paterson and Leadbetter (1999)
Identification of patient needs	Aggression should be understood as an expression of a need for the patient. Identifying and resolving that need may help avert violence.	Berring et al. (2016): multiple qualitative case studies ( $n = 42$ ) across a variety of clinical settings; this component was described in multiple cases ( $n = 5$ )	Bowers (2014); Dix and Page (2008); Kuivalainen et al. (2017); Price et al. (2018); Richmond et al. (2012)
Distraction	Distracting the person by changing the focus of the interaction may reduce their distress and decrease their arousal.	Hallet and Dickens (2015): qualitative study surveying medium secure unit staff ( $n = 72$ ); six core themes identified; this component was described by $n = 14$	NICE (2015b)
Negotiation	Identifying mutual goals and a shared consensus may consider underlying control issues as root cause of aggression.	Richmond et al. (2012): consensus statement at a national level	Dix and Page (2008); Duperouzel (2008); Mavandadi et al. (2016); NICE (2015b); Paterson and Leadbetter (1999)
Reframing events for patient	Emotions arise from an interpretation of an event that involves judgements about the motivation of others. Cautious exploration of alternative interpretations may prove helpful.	Price et al. (2018): qualitative interviews ( $n = 20$ ) with staff from five acute services; thematic analysis identified this component	
Non-confrontational limit setting	Explaining the situation calmly, where possible presenting the patient with a choice and avoiding issuing ultimatums.	Hallet and Dickens (2015): qualitative study surveying medium secure unit staff ( $n = 72$ ); 50% ( $n = 36$ ) described this specific component	NICE (2015b); Price and Baker (2012); Richmond et al. (2012); Richter (2006)

experience, subverting what may be the dominance of anger (Paterson and Leadbetter, 1999).

Key de-escalation components are considered in two authoritative guidelines. An American Association for Emergency Psychiatry consensus statement highlights a number of characteristics for effective de-escalation including: the establishment of verbal contact; not being provocative; being concise; listening closely to the patient; respecting their personal space; trying to agree or agree to disagree; offering choices and optimism; setting clear limits; identifying the wants or feelings of the patient; and debriefing the patient and staff (Richmond et al., 2012). In the UK, NICE Guideline NG10 highlights: establishing a working relationship; avoiding provocation; empathising and showing respect; assessing the situation; separating the patient; negotiating; distracting; non-confrontational limit-setting; self-regulatory procedures; and proactive de-escalation planning (NICE, 2015b). Table 2 summarises the interventional components of de-escalation emanating from a review of the literature and provides a brief explanation of each interventional component.

Where acute disturbance may be predictable in a known patient, it is suggested that individualised de-escalation plans should be developed in partnership with the patient, identifying their preferred responses with appropriate adaptations made where the patient has a sensory impairment (Austen, 2005; Department of Health, 2014). Where the patient is not known to staff, general components of de-escalation should be considered. A single member of staff should lead in communicating with the patient (NICE, 2015b; Richmond, et al., 2012). Consideration should be given to environmental change, but staff should remain mindful that the patient's needs for personal space may increase as arousal escalates (Turnbull et al., 1990). The exact nature of the de-escalation intervention will be informed by continual (risk) assessment, dynamic reflect-

ion and ongoing identification of the patient's needs; priorities may shift, evolve and fluctuate both during an individual incident and across time (Price et al., 2018; Richter, 2006).

Overall, there is widespread advocacy of de-escalation as an intervention (Department of Health, 2014; NICE, 2015b) with a number of theoretical conceptualisations of the process (Hallet and Dickens, 2017) and a variety of descriptions of the suggested components (Bowers, 2014; Dix and Page, 2008; Paterson and Leadbetter, 1999; Price and Baker, 2012). Nonetheless, there is a paucity of high-quality research evidence demonstrating the effectiveness of specific components of de-escalation.

## Benzodiazepines

All benzodiazepines share a common mechanism of action and produce a range of similar effects including anxiolytic, hypnotic, muscle relaxant and anticonvulsant. The individual benzodiazepine medications vary in their propensity for these effects depending on their potency and pharmacokinetics and this should inform the choice of benzodiazepine used for the indication (Baldwin et al., 2013). Benzodiazepines also vary in terms of their available formulations and this will further differ between countries; this is related to availability as well as the convenience of formulations (e.g. lorazepam injection requires refrigeration).

### Pharmacokinetics

When benzodiazepines are administered intramuscularly, T<sub>max</sub> is generally much shorter than for oral formulations (see Table 3); this can be helpful when a swift onset of action is important. However, T<sub>max</sub> for lorazepam is not much shorter for the IM formulation compared to the oral formulation. Further, lorazepam has a maximum licensed oral dose of 4 mg daily but despite bioequivalence

**Table 3.** Benzodiazepine formulations

Medication	Route	Formulation	Bioavailability	Time to maximum plasma concentration (T <sub>max</sub> )
Clonazepam	Oral	Tablets	90%	1–4 hours
	IM	Liquid Injection	90% 93%	1–4 hours 3 hours
Diazepam	Oral	Tablets	76%	30–90 minutes
		Liquid	76%	30–90 minutes
	IM IV	Injection Injection (emulsion)	Erratic 100%	Erratic ≤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

IM: intramuscular; IV: intravenous.



between oral and IM doses, the licensed IM dose can be much higher, as it is based on the weight of the patient (0.025–0.03 mg/kg every 6 hours; 1.75–2.1 mg for an average 70 kg man) (Pfizer Ltd, 2014). Oral lorazepam has a T<sub>max</sub> of 2 hours and there is no risk of accumulation on repeated dosing.

For midazolam injection, absorption is rapid and complete, with peak plasma concentration achieved within 30 minutes. It has a faster onset of action (5–20 minutes) than lorazepam and some antipsychotics (Baldaçara et al., 2011; Isbister et al., 2010; Martel et al., 2005; Nobay et al., 2004; TREC Collaborative Group, 2003). Unlike most other benzodiazepines, midazolam is water soluble hence it has a short half-life. In contrast, both diazepam and clonazepam have long half-lives and active metabolites, so multiple dosing is associated with a risk of accumulation and thus a risk of cumulative adverse effects.

### Oral

The efficacy of buccal midazolam has only been assessed in a small service evaluation ( $n = 27$ ) in which it was found to reduce agitation (measured indirectly using the Behavioural Activation Rating Scale) (Swift et al., 2002) in 70% of participants within 30 minutes (Taylor et al., 2008). Other oral benzodiazepines have also been used but data are very sparse; for example, Barbee et al. (1992) reported a single randomised double-blind trial for oral alprazolam plus oral haloperidol versus oral haloperidol alone ( $n = 28$ ) but alprazolam is not commonly used in the UK. Review of the literature did not reveal any studies evaluating oral lorazepam, clonazepam or diazepam as monotherapy; despite this, other guidelines still recommend the use of oral lorazepam (NICE, 2005; Wilson et al., 2012a).

### Oral versus intramuscular

A larger ( $n = 162$ ) trial by Currier et al. (2004) replicated findings from an earlier study ( $n = 37$ ; Foster et al., 1997) demonstrating that both oral and IM lorazepam had a similar clinically significant effect by 30 minutes after administration, with the effects of both lasting for at least 120 minutes, although this was based on combination arms of oral risperidone plus oral lorazepam versus IM haloperidol plus IM lorazepam. Therefore, there is no evidence of a clear time advantage in using IM lorazepam when a patient is willing to accept oral lorazepam. There is an absence of trial evidence comparing the oral and IM preparations of other benzodiazepines.

### Intramuscular monotherapy

Zaman et al. (2017) conducted a detailed review of the evidence and practice of using benzodiazepines for acute disturbance induced by psychosis; they included 20 RCTs (total  $n = 695$ ) but with no head-to-head studies. Overall, the evidence was weak and most of the trials were too small to highlight differences or to allow strong conclusions to be drawn to inform practice. The authors concluded that there was no difference in improvement in the medium term when benzodiazepines were compared to haloperidol ( $n = 188$ ; five RCTs; RR 0.89; 95% CI 0.71–1.11); and when benzodiazepines were compared to haloperidol plus promethazine, there was a higher risk of lack of improvement with benzodiazepines in the medium term ( $n = 200$ ; one RCT; RR 2.17; 95% CI 1.16–4.05; Zaman et al., 2017).

A Canadian review similarly concluded that the evidence for the comparative efficacy and safety of antipsychotics

### Box 1. Overview of TREC trials

There were four large RCTs, conducted in Brazil and India, that compared the effectiveness of a combination of IM haloperidol plus IM promethazine with a range of other IM strategies, namely: IM midazolam ( $n = 301$ ; TREC Collaborative Group 2003), IM lorazepam ( $n = 200$ , Alexander et al., 2004), IM haloperidol ( $n = 316$ , Huf et al., 2007) and IM olanzapine ( $n = 300$ , Raveendran et al., 2007). All trials recruited from psychiatric emergency rooms and, although primary outcomes differed between studies, all reported on whether the patient was tranquil or asleep at 15–20 minutes after administration of the trial medication. These studies have been criticised for using sleep as a desirable endpoint, but they remain the most methodologically robust studies of RT conducted in psychiatric settings. See Table 4 for a summary of the primary and secondary outcomes relating to sedation as measured by the composite outcome of being 'tranquil or asleep' as well as the outcome measure of being 'asleep'. Potentially serious adverse effects are also reported.

When considered together, the TREC studies lead to the conclusions that: (1) a combination of IM haloperidol plus IM promethazine is more rapidly effective than IM lorazepam or IM haloperidol alone, and as rapidly effective and with a longer lasting sedative effect than IM olanzapine; (2) only IM midazolam was more rapidly sedating than the combination of IM haloperidol plus IM promethazine but respiratory depression was noted in one patient in the midazolam group; (3) IM haloperidol alone was associated with an unacceptably high (6.4%) incidence of acute dystonia, in comparison to the combination of IM haloperidol plus IM promethazine, and this contributed to the decision to stop the trial early after the interim analysis. Based on these trials, it can be concluded that a combination of IM haloperidol 5–10 mg plus IM promethazine 25–50 mg is an effective and safe strategy for RT (Huf et al., 2016; NICE, 2015b). The TREC Collaborative Group (2003) conducted a post-hoc analysis for diagnosis (misusing substances vs psychosis) and found no difference in response to IM midazolam versus IM haloperidol plus IM promethazine.

**Table 4.** Summary of TREC trials

Trial publication	Treatment arms	Primary outcome results: tranquil or asleep	Secondary outcome results: tranquil or asleep	Secondary outcome results: asleep	Reported adverse effects
TREC Collaborative Group (2003)	IM M 7.5–15 mg ( <i>n</i> = 151) versus IM H 5–10 mg plus IM P 25–50 mg ( <i>n</i> = 150)	20 minutes: M: 89% HP: 67% (RR 1.32, 95% CI 1.16–1.49)	– 40 minutes M: 93%, HP: 83% 60 minutes M: 93%, HP: 87%, NS 120 minutes M: 95%, HP: 92%, NS	20 minutes M: 62%, HP: 29% 40 minutes M: 78%, HP: 46% 60 minutes M: 79%, HP: 55% 120 minutes M: 83%, HP: 63%	M: One transient respiratory depression, which was fully reversed by IV flumazenil (patient had alcohol, and possibly cocaine induced, aggression) HP: One grand mal seizure (had diagnosis of epilepsy)
Alexander et al. (2004)	IM L 4 mg ( <i>n</i> = 100) versus IM H 10 mg plus IM P 25–50 mg ( <i>n</i> = 100)	4 hours: L: 96% HP: 96% (RR 1.0, 95% CI 0.94–1.06, NS)	15 minutes L: 78%, HP: 89% (RR 1.1, 95% CI: 1.01–1.29) 30 minutes L: 81%, HP: 95% 60 minutes L: 90%, HP: 98% 120 minutes L: 88%, HP: 97%	15 minutes L: 5%, HP: 45% – 30 minutes L: 22%, HP: 69% 60 minutes L: 32%, HP: 67% 120 minutes L: 39%, HP: 69% 240 minutes L: 45%, HP: 76%	L: One 'moderate worsening of respiratory difficulty' in a patient with asthma and one nausea and dizziness
Huf et al. (2007)*	IM H 5–10 mg ( <i>n</i> = 156) versus IM H 5–10 mg plus IM P 25–50 mg ( <i>n</i> = 160)	20 minutes: H: 55% HP: 72% (RR 1.30, 95% CI 1.10–1.55)	– 40 minutes H: 76%, HP: 81%, NS 60 minutes H: 81%, HP: 87%, NS 120 minutes H: 89%, HP: 91%, NS	20 minutes H: 8%, HP: 19% 40 minutes H: 35%, HP: 36%, NS 60 minutes H: 49%, HP: 48%, NS 120 minutes H: 60%, HP: 61%, NS	H: Nine acute dystonia and one seizure HP: One seizure
Raveendran et al. (2007)	IM O 10 mg ( <i>n</i> = 150) versus IM H 10 mg plus IM P 25–50 mg ( <i>n</i> = 150)	15 minutes: O: 87% HP: 91% (RR 0.96, 95% CI 0.34–1.47, NS)	– 30 minutes O: 93%, HP: 96%, NS 60 minutes O: 94%, HP: 99% 120 minutes O: 94%, HP: 97%, NS 240 minutes O: 96%, HP: 97%, NS	15 minutes O: 43%, HP: 57% 30 minutes O: 63%, HP: 76% 60 minutes O: 66%, HP: 80% 120 minutes O: 61%, HP: 80% 240 minutes O: 59%, HP: 75%	O: Two akathisia, one nausea HP: One transient hypotension in a patient known to be dehydrated

\*This trial was discontinued early on ethical grounds due to the occurrence of 11 serious adverse events.

CI: confidence interval; H: haloperidol; HP: haloperidol+promethazine; IM: intramuscular; IV: intravenous; L: lorazepam; M: midazolam; NS: non-significant statistical difference as 95% confidence interval for relative risk includes the value of 1; O: olanzapine; P: promethazine; RR: relative risk; TREC: Tranquilização Rápida-Ensaio Clínico.

and benzodiazepines in RT was conflicting and inconclusive (CADTH, 2015). In essence, there are no large, well-designed trials of RT conducted in the UK; the largest RCTs used to inform the UK practice are the four Tranquilização Rápida-Ensaio Clínico (TREC) trials (Rapid Tranquillisation Clinical Trials) and only two of these included a benzodiazepine, see Box 1 and Table 4.

**Lorazepam.** Although relatively weak, there is more trial evidence for the use of IM lorazepam than for all other parenteral benzodiazepines (Zaman et al., 2017). IM lorazepam was evaluated in one of the TREC trials and was found to be effective but less rapidly so than the combination of IM haloperidol plus IM promethazine (see

Box 1 and Table 4) (Alexander et al., 2004). In a double-blind RCT (*n* = 201) IM lorazepam was less effective than IM olanzapine when measured on the Excited Component (subscale) of the Positive and Negative Syndrome Scale (PANSS-EC; Kay et al., 1987; Kay and Sevy, 1990) at 30, 60, 90 and 120 minutes (Meehan et al., 2001). IM lorazepam was found to be more sedating than IM aripiprazole at 2 hours (Zimbroff et al., 2007).

**Midazolam.** A number of trials have demonstrated the efficacy of the parenteral formulation as a sole RT agent, including one of the TREC trials (TREC Collaborative Group, 2003). IM midazolam leads to a quicker time to sedation than IM lorazepam or IM haloperidol (Nobay et

al., 2004). In one RCT on RT comparing standard doses (10 mg or below) with high doses (above 10 mg) of IM droperidol, IM midazolam, IM haloperidol or IM droperidol plus IM midazolam, the median time to sedation was 20 minutes in both dose groups and it concluded that a high dose did not result in more rapid or effective sedation, but was associated with double the incidence of side effects compared with standard doses (Calver et al., 2013).

In a further RCT ( $n = 144$ ) there were more participants in the IM ziprasidone group who remained acutely disturbed at 15 minutes than in the IM midazolam and IM droperidol groups respectively ( $p = 0.01$ ), but there was no difference in the number of participants remaining acutely disturbed at 30 minutes ( $p = 0.08$ ), and at 45 minutes more of those in the midazolam group were more acutely disturbed than in the IM droperidol and IM ziprasidone groups ( $p = 0.03$ ), highlighting that action of IM midazolam was rapid but not sustained (Martel et al., 2005). Another trial similarly highlighted the problematic short half-life for IM midazolam with its clinical effects not lasting as long as IM haloperidol or IM lorazepam; times to arousal were reported as 81.9 minutes for IM midazolam, 126.5 minutes for IM haloperidol and 217.2 minutes for IM lorazepam (Nobay et al., 2004). Its short half-life was also linked to the need for repeated doses; 62% receiving IM midazolam required additional sedation as compared with IM midazolam plus IM droperidol (41%) or IM droperidol alone (33%) (Isbister et al., 2010). In an RCT conducted in Brazil, 70% of the participants receiving IM midazolam plus IM haloperidol required mechanical restraint, which was significantly higher than for the other treatment arms: IM ziprasidone (33%), IM haloperidol alone (20%), IM haloperidol plus IM promethazine (17%), IM olanzapine (3%) (Baldaçara et al., 2011).

*Others.* There is no relevant evidence of efficacy for IM diazepam in RT. In a very small double-blind trial ( $n = 16$ ) IM clonazepam was effective but slower acting than IM haloperidol (Chouinard et al., 1993). One small study ( $n = 28$ ) assessed IM flunitrazepam for RT and found it to be as effective at 30 minutes as IM haloperidol was in reducing the Overt Aggression Score (OAS; Yudofsky et al., 1986) ( $F = 72.42$ ;  $df = 6, 156$ ;  $p < 0.001$  time effect) but its effects were short lasting and wore off by 60 minutes (Dorevitch et al., 1999).

#### *Intramuscular benzodiazepines in combination with other medications*

*Benzodiazepines plus haloperidol.* A recent meta-analysis included 20 RCTs (with 695 participants) testing benzodiazepines alone or in combination with other agents for acute disturbance due to psychosis (Zaman et al., 2017). The conclusion was that trials comparing IM

benzodiazepines plus antipsychotics versus IM benzodiazepines alone did not yield results with clear differences; this was very low-quality evidence. In the short term (15 mins to 1 hour), IM lorazepam plus IM haloperidol was found to be more sedative than lorazepam only ( $n = 47$ ; one RCT; RR 1.92; 95% CI 1.10–3.35), although there was no difference in the medium term (1–48 hours); this was low-quality evidence (Zaman et al., 2017).

In trials comparing the combination of a benzodiazepine plus an antipsychotic versus the same antipsychotic alone (the antipsychotic in all trials was IM haloperidol, which was combined with a variety of benzodiazepines), there was no difference in the improvement observed in the medium term ( $n = 185$ ; four RCTs; RR 1.17; 95% CI 0.93–1.46); this was low-quality evidence. Yet sedation was more common in the participants who received the combination, in both the short term ( $n = 45$ ; one RCT; RR 2.25; 95% CI 1.18–4.30) and the medium term ( $n = 172$ ; three RCTs; RR 1.75; 95% CI 1.14–2.67); this was very low-quality evidence (Zaman et al., 2017).

Of note, one small trial compared IM midazolam plus IM haloperidol versus IM promethazine plus IM haloperidol. Although medium-term sedation was higher in the IM midazolam plus IM haloperidol group ( $n = 60$ ; one RCT; RR 12.00; 95% CI 1.66–86.59), the same group was also at a higher risk of showing no clinical improvement (global state) ( $n = 60$ ; one RCT; RR 25.00; 95% CI 1.55–403.99); this was very low-quality evidence (Zaman et al., 2017).

Another meta-analysis (Ostinelli et al., 2017), with a focus on the use of haloperidol in RT, reviewed two studies that compared IM haloperidol alone versus IM haloperidol plus IM lorazepam ( $n = 113$ ) and one study where the adjunct benzodiazepine was IM midazolam ( $n = 60$ ). Significantly more of the participants receiving IM lorazepam plus IM haloperidol were asleep after 3 hours ( $n = 67$ ; one RCT; RR 1.83; 95% CI 1.11–3.02); fewer participants in the combination group required more than one additional injection ( $n = 67$ ; one RCT; RR 1.05; 95% CI 0.87–1.27); and by 30 minutes more participants showed overall improvement ( $n = 45$ ; one RCT; RR 2.67; 95% CI 1.25–5.68), a difference that was not sustained; this was very low-grade evidence. For the combination of midazolam plus haloperidol, no advantage was found; this was very low-grade evidence with only one small study ( $n = 60$ ) (Ostinelli et al., 2017).

Although both meta-analyses above reviewed much of the available evidence, two studies merit further mention here. Baldaçara et al. (2011) concluded that the combination of IM midazolam plus IM haloperidol showed the worst results across a range of observed parameters. Calver et al. (2013) conducted a prospective study of parenteral sedation for acute disturbance ( $n = 171$ ). High-dose medication was not associated with more rapid sedation than

standard dosage. Just over half of the participants (54%) were prescribed high-dose medication and, in the majority of these cases, the medication was a combination of IM midazolam plus an IM antipsychotic (droperidol or haloperidol).

*Benzodiazepine plus promethazine.* There is no trial evidence that we are aware of that specifically evaluated the combination of IM lorazepam plus IM promethazine.

#### *Intravenous*

Intravenous midazolam is sometimes used for RT in an emergency department setting. An RCT of 153 participants with acute disturbance found IV midazolam to be more rapidly sedating than IV droperidol, but three participants in the IV midazolam arm required active airway management (Knott et al., 2006). A subsequent study found that IV midazolam 2.5–5 mg alone was more likely to result in treatment failure, due to the need for additional sedation, than either combination of IV droperidol 5 mg plus IV midazolam 2.5–5 mg or IV olanzapine 5 mg plus IV midazolam 2.5–5 mg; there was no difference in adverse effects between the three treatment arms ( $n = 336$ ; Chan et al., 2013).

IV lorazepam was compared with IV droperidol in a randomised 1 hour open-label trial ( $n = 202$ ); both were effective in achieving sedation within 30 minutes although IV droperidol produced sedation more rapidly than IV lorazepam. However, fewer repeat doses of IV droperidol were required compared with IV lorazepam at 30 minutes. Participants in both arms did not require airway intervention (Richards et al., 1998).

An older study (Lerner, 1979) investigated the efficacy of IV diazepam (30–40 mg) versus IV haloperidol (20–35 mg) over a period of time and not as RT; however, these doses are high compared with current practice. The published data on IV diazepam for acute disturbance are very limited. One article describes a survey of emergency prescribing in a general hospital where medication was given intravenously for 53 out of 102 incidents (Pilowsky et al., 1992). IV diazepam alone or in combination with IV haloperidol appeared to be more predictably and rapidly effective than other medications given intramuscularly. However, if used in clinical practice, the long half-life of diazepam and associated risk of accumulation should be borne in mind. Furthermore, it is important to use the emulsified formulation of diazepam (Diazemuls®) and not the aqueous solution for IV administration as the latter carries a greater risk of adverse effects. If used, Diazemuls should be administered slowly (1.0 ml solution per minute) with the patient kept supine for at least an hour afterwards.

A retrospective study, using historic controls, evaluated the impact of a structured IM sedation protocol, which had replaced the previous practice of IV sedation (Calver et al.,

2010). The median duration of acute disturbance using the IM protocol was 21 minutes ( $n = 58$ ; range 5–78 mins) while the median duration using the IV approach was 30 minutes ( $n = 79$ ; range 5–135 mins); this difference was statistically significant ( $p = 0.03$ ). Hence IV medication did not appear to offer an advantage over IM in terms of time to effect.

#### *Adverse effects*

The adverse effects of benzodiazepines include, but are not limited to, over-sedation, drowsiness, ataxia and potentially cardiovascular collapse, hypotension with the associated risk of falls and ultimately loss of consciousness. Disinhibition can also occur with benzodiazepines although this is probably uncommon (Paton, 2002). All benzodiazepines can cause respiratory depression and this is more likely with parenteral rather than oral dosing, increasing dosage and with benzodiazepines that are more likely to accumulate on repeated administration, such as diazepam.

IM midazolam has been found to be more sedating than IM lorazepam, with an increased risk of respiratory depression (Nobay et al., 2004), and more sedating than IM antipsychotics alone or in combination with IM promethazine (Baldaçara et al., 2011; TREC Collaborative Group, 2003). In one RCT ( $n = 91$ ) with three arms, participants who received IM midazolam alone had more treatment failures with additional sedation being required (Isbister et al., 2010). In the same trial 28% of participants receiving IM midazolam experienced oxygen desaturation or airway obstruction compared with 6% for those given IM droperidol and 4% for the combination of IM droperidol plus IM midazolam. Thus, a significant safety concern limits the utility of midazolam as a safe IM RT option and it is not widely recommended (NICE, 2015b). Furthermore, concerns have been raised around the risk of

#### **Box 2.** Flumazenil

Flumazenil is a benzodiazepine antagonist (reversal agent) which is administered intravenously and should be used if the respiratory rate falls below 10 breaths/minute or oxygen saturation falls below 90%, due to use of benzodiazepines.

Dose: 200 µg intravenously over 15 seconds. If required level of consciousness is not regained, then 100 µg intravenously every 1/ minute as required. Usual dose 300–600 µg; maximum 1 mg per course or in 24 hours.

Precautions: Flumazenil is contraindicated in patients with epilepsy who are receiving long-term benzodiazepines. Flumazenil has a short half-life therefore subsequent doses may be necessary; keeping in mind that benzodiazepine effects may persist for at least 24 hours. If respiratory rate does not normalise with doses of flumazenil, urgently consider other causes of sedation.



overdose with midazolam injection in adults when used for conscious sedation, leading to a 2008 National Patient Safety Agency Rapid Response Report recommending that stocks of flumazenil (see Box 2) be available where parenteral midazolam is used (NPSA, 2008a, b). We would extend this recommendation to include immediate access to flumazenil wherever parenteral benzodiazepines are prescribed (Joint Formulary Committee, 2018). IV midazolam was associated with the need for active airway management in one study (Knott et al., 2006) whereas this was not the case for IV lorazepam (Richards et al., 1998).

### *From evidence to practice*

**Recommended.** Buccal midazolam has evidence from a small service evaluation that it is effective. Oral lorazepam may be effective, based on data of its use in combination with an antipsychotic, but it does not have any direct trial evidence to support its use as monotherapy. IM lorazepam alone is effective as highlighted by one of the TREC trials. The combination of IM lorazepam plus IM haloperidol has been evaluated in meta-analyses and found to be effective, although a baseline ECG is advised before haloperidol use (in any formulation) due to the risk of QTc prolongation.

Parenteral benzodiazepines have safety concerns due to the risk of respiratory depression and, as flumazenil can reverse this it must be immediately available wherever parenteral benzodiazepines are used. Due to the potential risk of both respiratory depression and cardiac adverse effects, RT IV options must only be used in settings where resuscitation equipment and trained clinicians are available to manage medical emergencies. In this setting, both IV midazolam and IV lorazepam are effective as evidenced by trial data, but the immediate availability of flumazenil must first be confirmed.

**Not recommended.** Oral clonazepam has no evidence of effectiveness as monotherapy and it is associated with the risk of accumulation with repeated dosing and the resultant risk of cumulative adverse effects. IM midazolam as monotherapy had good evidence of initial effectiveness but this is not sustained over time due to its short half-life and, importantly, it also carries a risk of respiratory depression. The evidence for IM clonazepam was based on only a very small study. No trial evidence was found that evaluated the combination of IM lorazepam plus IM promethazine. All formulations of diazepam carry the risk of accumulation and at best have only poor-quality evidence for use in RT.

## **Common antipsychotics**

All antipsychotics act on dopamine receptors, usually but not always as dopamine-2 (D2) antagonists. Most also act on other receptors. Antipsychotics vary in their propensity

for their various effects depending on their potency and pharmacokinetics. Antipsychotics also vary in terms of their available formulations and this will also differ between countries. When used in the treatment of acute psychotic relapse, antipsychotics are more effective than placebo in reducing psychotic symptoms overall and in reducing acute disturbance as measured using the PANSS-EC subscale (Garriga et al., 2016).

### *Pharmacokinetics*

For general pharmacokinetic considerations see above (De-escalation and rapid tranquillisation). It is commonly believed that oro-dispersible formulations of risperidone and olanzapine are more rapidly absorbed than conventional tablets but this is not the case; T<sub>max</sub> for both oral and oro-dispersible risperidone is 1–2 hours (Janssen-Cilag, 2017), whereas T<sub>max</sub> for both formulations of olanzapine is 5–8 hours (Eli Lilly, 2017a). However, oro-dispersible preparations dissolve very quickly in saliva rendering covert non-adherence more difficult.

For oral haloperidol T<sub>max</sub> is 2–6 hours but for IM haloperidol T<sub>max</sub> is 20 minutes. The IM dose required to give the same plasma concentration as any given oral dose is approximately 30% lower and this is due to the difference in the magnitude of first pass liver metabolism. T<sub>max</sub> for IM aripiprazole is 1 hour and for IM olanzapine 15–45 minutes (see Table 5). Values for other drugs not listed in the table can be obtained from the Summary of Product Characteristics (SmPC) for the individual drug, available at <https://www.medicines.org.uk>. Note that these data are mostly derived from phase I and II clinical trials and are applicable to working-age adults with normal muscle mass and levels of activity, who have normal liver function and are not prescribed any interacting medicines. In clinical practice, patients who receive RT may vary considerably in terms of age, level of activity and use of substances and alcohol.

All antipsychotic medications used in RT (or their active metabolites) have elimination half-lives of 20 hours or more. Multiple administrations will lead to accumulation that places the patient at risk of adverse effects.

### *Oral*

Garriga et al. (2016) reviewed 26 trials for oral antipsychotics in the treatment of acute disturbance including: one assessing oral first-generation antipsychotics (FGAs), four comparing FGAs with second-generation antipsychotics (SGAs) and 21 assessing SGAs. They concluded that there was no real difference in the efficacy for SGAs as compared to FGAs, either when used alone or in combination with lorazepam. However, most of these trials were not carried out in the acute treatment of agitation and endpoint measurements were at weeks or months rather than hours or days. A subsequent scoping review concluded

**Table 5.** Antipsychotic formulations

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

IM: intramuscular; IV: intravenous.

there is a surprisingly small amount of evidence regarding oral antipsychotics for acute disturbance (Mullinax et al., 2017). Only two studies assessed the efficacy and tolerability of oral olanzapine in the treatment of psychotic acute disturbance. In the first study ( $n = 87$ ), oro-dispersible tablets were compared to risperidone oral solution (Hatta et al., 2008) and both drugs were equally effective in reducing PANSS-EC scores with no difference in requiring additional injections due to worsening. The second study was a randomised, double-blind trial over five days ( $n = 604$ ), which evaluated oral olanzapine versus oral aripiprazole and reported significant improvements in PANSS-EC scores but no difference in the treatment groups; however, a greater proportion of participants receiving aripiprazole also required adjunct lorazepam (Kinon et al., 2008).

There is some literature supporting the use of oral risperidone in the management of acute disturbance. In an RCT ( $n = 162$ ) of a single dose of oral risperidone plus oral lorazepam compared to IM haloperidol plus IM lorazepam, the mean PANSS-EC scores at 30, 60 and 120 minutes after dosing were statistically significantly improved at each time point compared to baseline ( $p < 0.0001$ ) in both groups with no difference between the groups (Currier et al., 2004). A study ( $n = 226$ ) focusing on acute disturbance in psychosis compared the use of oral risperidone plus oral lorazepam versus IM FGAs with or without adjunct IM lorazepam and found that not only was oral risperidone plus oral lorazepam more successful at two hours but also the incidence of extrapyramidal symptoms (EPS) was lower than with the IM medications (Lejeune et al., 2004).

Wilhelm et al. (2008) reported that oral risperidone was associated with improvement in PANSS-EC scores over a 5-day period but that oral risperidone use was usually (72%) associated with concomitant benzodiazepine use. Another study compared oro-dispersible risperidone versus IM haloperidol in a randomised open prospective study found the PANSS-EC score significantly decreased over time in both treatment groups without any significant group difference (Lim et al., 2010). In a small RCT ( $n = 42$ ) with four treatment arms, Hsu et al. (2010) also found that scores for PANSS-EC and Agitation–Calmness Evaluation Scale (ACES; Meehan et al., 2002) improved over 24 hours for participants receiving an oral solution of risperidone 3 mg.

There is some evidence supporting the use of oral quetiapine to reduce agitation, but these studies are over 6 weeks (Chengappa et al., 2003) or a year (Volavka et al., 2011). One small study ( $n = 36$ ) conducted over 5 days (Ganesan et al., 2005) suggested effectiveness of quetiapine in acute disturbance as mean scores reduced on the OAS.

Very little evidence has been published regarding oral haloperidol. Trials in which it has been evaluated were over 8 weeks in duration (Higashima et al., 2004) or in combination with IM lorazepam (Veser et al., 2006). One prospective, rater-blinded study ( $n = 101$ ) over 72 hours compared oral SGAs (risperidone, olanzapine and quetiapine) versus oral haloperidol and reported effectiveness for all four treatments with decreases in scores of the hostility-suspiciousness factor derived from the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and Modified Overt Aggression Scale (Kay et al., 1988),

with no significant differences between the groups. However, EPS were more common in the haloperidol group (21.4%) than in the risperidone (7.4%), olanzapine (0%) or quetiapine (0%) groups (Villari et al., 2008).

#### *Oral versus intramuscular*

A number of small studies have explored the relative effectiveness of oral and IM antipsychotic medications in the management of psychotic agitation and found little difference between them. For example, the relative effectiveness of oral risperidone plus oral lorazepam and IM haloperidol plus IM lorazepam was reviewed by Currier and Medori (2006), who concluded that these strategies were equally effective.

A small study ( $n = 42$ ) found that participants who received IM olanzapine or oral disintegrating olanzapine tablets showed significantly greater improvements in PANSS-EC scores when compared with those administered IM haloperidol (Hsu et al., 2010). A naturalistic study that tracked clinical practice after oro-dispersible olanzapine was made available for general use (Simpson et al., 2006) found that this did not result in any change in the prevalence of use of restrictive interventions (IM medication, seclusion or restraint).

A recent review by Mullinax et al. (2017) of trials evaluating oral antipsychotics for participants with acute disturbance found only six small studies ( $n = 464$ ; range 20–162), five of which compared oral SGAs to either IM FGAs or IM SGAs. In general, the studies found that oral SGAs were effective for reducing acute disturbance and had side-effect profiles that were comparable to those of FGAs (Mullinax et al., 2017).

#### *Intramuscular monotherapy*

A review of RCTs (most of which were placebo-controlled licensing studies) of parenteral formulations of SGAs for psychotic acute disturbance concluded that, for 'response at 2 hours' the numbers needed to treat were three for IM olanzapine and five for IM aripiprazole (Citrome, 2007).

**Haloperidol.** The efficacy and safety of haloperidol, by any route, for psychosis-induced acute disturbance has been considered in a Cochrane review (Ostinelli et al., 2017). Many comparisons are reported on and the main results highlight that haloperidol, as compared with placebo, does cause sedation in that more participants are asleep at 2 hours. Compared with those participants receiving IM aripiprazole, those given IM haloperidol required fewer injections ( $n = 473$ ; two RCTs; RR 0.78; 95% CI 0.62–0.99; low-quality evidence). When compared to those given IM lorazepam there was no difference in the proportion asleep at 1 hour (one RCT;  $n = 60$ ; RR 1.05; 95% CI 0.76–1.44; very low-quality evidence). There were clear concerns raised in a number of studies regard-

ing the propensity of haloperidol to cause acute dystonia, and the authors concluded that where additional drugs are available, sole use of haloperidol for extreme emergency could be considered unethical. Adjunct promethazine for haloperidol has higher-quality evidence from RCTs as outlined below (see Intramuscular antipsychotics in combination with other medications).

**Olanzapine.** One RCT ( $n = 150$ ) compared IM olanzapine, IM ziprasidone, IM haloperidol, IM haloperidol plus IM promethazine, and IM haloperidol plus IM midazolam and found no large differences between these treatment arms with respect to efficacy (Baldaçara et al., 2011). A systematic review and meta-analysis of the efficacy and safety of IM olanzapine for the management of acute disturbance, including RT, concluded that IM olanzapine and IM haloperidol were equally effective but the former was better tolerated with respect to EPS and was associated with marginally less QT prolongation (Kishi et al., 2015). A Cochrane review, which addressed psychosis-induced acute disturbance, concluded that IM olanzapine is rapidly effective but more likely to result in subsequent injections being required than the combination of IM haloperidol plus IM promethazine recommended by NICE (Huf et al., 2016; NICE, 2015b). A large prospective observational study of the use of parenteral olanzapine in an acute hospital setting reported that 1% (5 of 489) of participants who received olanzapine IM required intubation (Cole et al., 2017).

**Droperidol.** Droperidol is a butyrophenone antipsychotic with a similar pharmacology to haloperidol, although it is more sedative. Droperidol, both orally and parenterally, was commonly used for the management of acute disturbance in psychiatric settings in the UK until it was withdrawn from use in 2001 due to an association with QTc prolongation (Meyer, 2003; Reilly et al., 2000). Continuing interest in the use of droperidol for RT, particularly in Australia, has prompted a number of recent RCTs.

In a blinded trial, 91 acutely disturbed participants who were seen in general hospital medical emergency departments in Australia were randomised to receive IM droperidol (10 mg), IM midazolam (10 mg) or a combination of IM droperidol (5 mg) plus IM midazolam (5mg) (Isbister et al., 2010). The primary outcome was the duration of acute disturbance and this did not differ across treatment arms, although it was noted that IM midazolam alone required additional sedation more often than the other two treatment arms. Having determined that IM droperidol alone was as effective as and safer than IM midazolam in this small RCT, safety was further explored in a large prospective observational study, again in general hospital emergency departments. Of 1009 participants who received parenteral (IM or IV) droperidol 10 mg and

where a post-administration ECG was possible, just 13 participants (1.3%) had evidence of QTc prolongation, and in half of these cases other prescribed medicines are likely to have contributed. There were no cases of torsades de pointes (Calver et al., 2015b).

A further blinded RCT conducted in a psychiatric intensive care unit (PICU) in Australia compared IM droperidol 10 mg ( $n = 118$ ) with IM haloperidol 10 mg ( $n = 110$ ) and the median time to sedation was 20 minutes for IM haloperidol and 25 minutes for IM droperidol (not statistically significant, Calver et al., 2015a). More additional sedation was required in those randomised to the IM haloperidol arm and more adverse effects, mainly hypotension, were seen in the IM droperidol arm. A Cochrane review, which did not differentiate between IM and IV routes, concluded that droperidol is effective and can be used to manage acute disturbance caused by psychosis (Khokhar and Rathbone, 2016).

**Aripiprazole.** A recent Cochrane review evaluated three poor-quality studies ( $n = 885$ ) that compared IM aripiprazole versus placebo or IM haloperidol or IM olanzapine (Ostinelli et al., 2018). When aripiprazole was compared with placebo, fewer injections were required (RR 0.69; 95% CI 0.56–0.85) and clinically important improvement in acute disturbance favoured the IM aripiprazole group at 2 hours (RR 1.50; 95% CI 1.17–1.92) with more participants experiencing adverse effects in the IM aripiprazole group (RR 1.51; 95% CI 0.93–2.46). When IM aripiprazole was compared with IM haloperidol, more injections were required ( $n = 477$ ; two RCTs; RR 1.28; 95% CI 1.00–1.63) with no significant difference in agitation (RR 0.94; 95% CI 0.80–1.11). When compared with IM olanzapine, IM aripiprazole was less effective in reducing agitation at 2 hours (RR 0.77; 95% CI 0.60–0.99) and there was no difference in adverse effects apart from participants allocated to IM aripiprazole experiencing less somnolence (RR 0.25; 95% CI 0.08–0.82). Another double-blind, placebo-controlled trial ( $n = 357$ ) evaluated IM aripiprazole and IM haloperidol, and both groups showed significant changes in PANSS-EC and ACES compared with placebo, although IM aripiprazole showed significant changes earlier (Tran-Johnson et al., 2007). In a further double-blind RCT for 301 acutely agitated inpatients, sedation during the first 2 hours was greater with IM lorazepam compared with IM aripiprazole but improvement in PANSS-EC scores was similar at 2 hours (Zimbroff et al., 2007).

*Intramuscular antipsychotics in combination with other medications*

**Haloperidol plus promethazine.** The evidence for IM haloperidol plus IM promethazine comes from the meth-

odologically robust TREC trials on RT (see Box 1 and Table 4). When the TREC trials are considered together, it can be concluded that a combination of IM haloperidol plus IM promethazine is more rapidly effective than IM lorazepam or IM haloperidol alone, as rapidly effective as IM olanzapine, with IM haloperidol plus IM promethazine having a longer-lasting sedative effect and IM olanzapine requiring more additional drugs. Adding two further trials (Baldacara et al., 2011; Mantovani et al., 2013) to the evidence of the TREC trials, a Cochrane review (Huf et al., 2016) concluded that IM haloperidol and IM promethazine was effective and safe, and its use was based on good evidence. For IM haloperidol plus IM promethazine versus IM haloperidol alone, the combination was clearly more effective ( $n = 316$ ; one RCT; RR 0.65; 95% CI 0.49–0.87).

A recent meta-analysis (Ostinelli et al., 2017), which focused on the use of haloperidol in RT, described two studies comparing IM haloperidol versus IM haloperidol plus IM promethazine ( $n = 376$ ). Significantly more participants in the combination group were tranquil or asleep by 20 minutes ( $n = 316$ ; RR 1.60; 95% CI 1.18–2.16). The relative risks were still in favour of the combination at 40, 60 and 120 minutes, but these were not statistically significant. The combination needed less repeat RT at 2 hours ( $n = 376$ ; two RCTs; RR 0.78; 95% CI 0.43–1.41). Of note, the authors of this meta-analysis also commented on the propensity of haloperidol alone to cause adverse effects. The adverse effect of dystonia caused by haloperidol was not offset by the addition of lorazepam ( $n = 67$ ; one RCT; RR 8.25; 95% CI 0.46–147.45; very low quality of evidence). However, based on the study by Huf et al. (2007), which had a high relative risk for acute dystonia in the IM haloperidol group ( $n = 316$ ; RR 19.48; 95% CI 1.14–331.92), there is an indication of a protective effect of IM promethazine when given in combination with IM haloperidol (Ostinelli et al., 2017).

**Haloperidol plus lorazepam.** Two recent meta-analyses have reviewed the combination of haloperidol plus lorazepam. Zaman et al. (2017) reviewed RCTs of benzodiazepines alone or in combination with other agents for acute disturbance due to psychosis, which included 20 trials with 695 participants. The review concluded there were no clear differences between IM benzodiazepines plus antipsychotics versus IM benzodiazepines alone; this was very low-quality evidence. Ostinelli et al. (2017) focused on the use of haloperidol in RT and described two studies that provided very low-grade evidence in favour of IM haloperidol plus IM lorazepam versus IM haloperidol ( $n = 113$ ), and one study where the adjunct benzodiazepine was IM midazolam (see Intramuscular benzodiazepines in combination with other medications, above).



### *Intravenous*

As the skills and equipment required to administer sedative medication IV are unlikely to be available in psychiatric settings, the routine use of IV medication in such settings cannot be recommended. Use in exceptional circumstances should be restricted to settings where resuscitation facilities are available and staff are trained to manage medical emergencies, such as in an emergency department.

**Droperidol.** A Cochrane review, which did not differentiate between IM and IV routes but did include three trials on IV droperidol, concluded that droperidol is effective and can be used to manage acute disturbance caused by psychosis (Khokhar and Rathbone, 2016).

Three large Australian RCTs conducted in emergency departments have examined the relative efficacy and safety of a number of IV strategies, and the first two were included in the Cochrane review. The first RCT found IV midazolam 5 mg to be more rapidly sedating than IV droperidol 5 mg, with three participants in the IV droperidol arm developing dystonia ( $n = 153$ ; Knott et al., 2006). The second RCT reported that IV midazolam 2.5–5 mg alone was more likely to result in treatment failure (i.e. a need for additional sedation) than either of the two comparator combinations of IV midazolam plus IV droperidol 5 mg or IV midazolam plus IV olanzapine 5 mg; no differences in adverse effects were seen for the three treatment arms ( $n = 336$ ; Chan et al., 2013). The third RCT reported that the combination of IV midazolam 5 mg plus IV droperidol 5 mg resulted in more rapid sedation but also in more cases of respiratory events than either IV droperidol 10 mg alone or IV olanzapine 10 mg; there were seven reported cases of QTc prolongation across all three treatment arms ( $n = 349$ ; Taylor et al., 2017). Subsequent subgroup analysis of the third trial focusing on management of methamphetamine-induced agitation found similar results (Yap et al., 2017). In an older randomised study ( $n = 202$ ), IV droperidol was associated with more rapid sedation, also requiring less repeat dosing than IV lorazepam (Richards et al., 1998).

**Olanzapine.** IV olanzapine was the focus of two studies conducted in emergency departments. One was a retrospective cohort study of 713 patients receiving IV olanzapine in the emergency department, including 177/265 (66.8%) of patients for whom adequate sedation was achieved with a single dose of IV olanzapine. However, 10% of the total sample of patients developed hypoxia with oxygen saturation  $< 92\%$  and seven patients (1%) required intubation (Martel et al., 2016). The other was a prospective observational study of acutely disturbed patients and respiratory depression occurred in 3.7% of those receiving IV olanzapine ( $n = 295$ ) with two requiring

intubation, and in 2.0% for IM olanzapine ( $n = 489$ ) with five requiring intubation (Cole et al., 2017).

**Haloperidol.** Only one study has been found for haloperidol ( $n = 136$ ), which included participants receiving IV administration ( $n = 19$ ) for acute disturbance; however, this study did not report its findings separately for the different routes other than to comment that the IV route required repeated dosing more often than IM or oral routes (Clinton et al., 1987). No RCTs of IV haloperidol have been published. Haloperidol carries a risk for QT prolongation, but the assertion that IV haloperidol is more likely to cause adverse cardiovascular effects may be confounded by its primary use in medically ill populations (Beach et al., 2017) and therefore an ECG is recommended before its use. In cases where IV administration is judged to be clinically necessary, this should be done only under continuous ECG monitoring for the detection of QT prolongation and severe cardiac arrhythmias.

### *Adverse effects*

Adverse effects are frequently dose related with higher doses and combinations having higher risks. One prospective observational study (Calver et al., 2013) compared a high dose (above 10 mg) with a standard dose (10 mg and below) of IM haloperidol, IM droperidol or IM midazolam and reported that high-dose sedation did not result in more rapid or effective sedation but was associated with double the incidence of side effects of standard doses, specifically hypotension and oxygen desaturation. Symptomatic hypotension has been reported with the co-administration of IM olanzapine and IM benzodiazepines (Zacher and Roche-Desilets, 2005). The manufacturer of olanzapine has cautioned against combining IM olanzapine with IM benzodiazepines (<http://www.palliativedrugs.org/download/SafetyLetterzyprexa.pdf>). However, a retrospective case series reported IM olanzapine was safe when given in combination with a benzodiazepine in patients who had not ingested alcohol; where alcohol had been consumed the combination of IM olanzapine and an IM benzodiazepine was associated with oxygen desaturation (Wilson et al., 2012b).

Antipsychotics can also cause EPS (Barnes et al., 2011). Some develop over time with repeated doses, but others can develop acutely, including oculogyric crises and acute dystonic reactions. Restlessness associated with akathisia can resemble agitation and therefore may lead to further doses being administered. IM haloperidol, when administered alone, has a greater propensity to cause acute EPS (Satterthwaite et al., 2008) and therefore its use as a single agent is not recommended (Ostinelli et al., 2017) but, if it is, an anticholinergic such as IM procyclidine can be prescribed for the treatment of acute dystonia (Taylor et al., 2015.)

Some antipsychotics, particularly parental haloperidol

and droperidol, are known to increase the QTc on the ECG, even at therapeutic doses. A QTc of greater than 500 ms is associated with an increased risk of torsades de pointes (Glassman and Bigger, 2001; Haddad and Anderson, 2002; Taylor, 2003). It is therefore advised, as the licence for haloperidol recommends, that a baseline ECG should be available before administering IM haloperidol (Concordia International, 2017). Consequently, as it is often not possible in the scenario of acute disturbance to carry out an ECG, and if one has not been done recently, haloperidol alone should be avoided.

Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex associated with all antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with all antipsychotics (see SmPC on <https://www.medicines.org.uk>). If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic active substances must be discontinued and supportive measures ensured (Su et al., 2014; Taylor et al., 2015).

#### *From evidence to practice*

**Recommended.** Oral formulations of aripiprazole, olanzapine and risperidone all have trial evidence supporting their effectiveness. Oral haloperidol and oral quetiapine both have some evidence of effectiveness. IM antipsychotic monotherapy options include IM aripiprazole and IM droperidol as both have good trial evidence supporting their use. IM olanzapine also has good evidence of efficacy as confirmed by one of the TREC trials, but it should only be administered by itself and not concurrently with IM benzodiazepines due to risk of hypotension; thus, there should be an interval of at least 1 hour between the two. The combination of IM haloperidol plus IM promethazine has been evaluated in meta-analyses, which included the TREC trials, and this combination has been found to be effective. Similarly, meta-analyses have also confirmed the efficacy of the combination of IM lorazepam plus IM haloperidol.

Due to the potential risk of both respiratory depression and adverse cardiac effects, RT IV options must only be used in settings where resuscitation equipment and trained clinicians are available to manage medical emergencies. In this setting, IV droperidol is effective as supported by trial evidence. IV olanzapine also has evidence of effectiveness but caution is advised due to the risk of respiratory depression and the lack of reversing agent. A baseline ECG is advised before use of haloperidol and droperidol in any formulation, as both are associated with a risk of QTc prolongation.

**Not recommended.** Although IM haloperidol monotherapy has evidence of effectiveness, measures are required to

offset its adverse effects; this is especially true for its risk of acute dystonia, which can be somewhat ameliorated by the use of adjunct IM promethazine. IV haloperidol has a lack of evidence for its use in RT.

## **Other interventions**

### *Promethazine*

Promethazine is a sedating antihistamine with anticholinergic effects. It is from the phenothiazine family and differs structurally from antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution (Babe and Serafin, 1996). In the UK, oral promethazine is available over the counter without prescription and is licensed for symptomatic treatment of allergic conditions and anaphylaxis, sedation and treatment of insomnia (Joint Formulary Committee, 2017). Promethazine acts as a strong antagonist at histamine H1 receptors, as a moderate antagonist at muscarinic receptors and weak/moderate antagonist at serotonin (5HT2A and 5HT2C), D2 and adrenergic  $\alpha$ -1 receptors (NLM Toxnet, 2018). Its onset of sedative effect ranges from 20–30 minutes (oral and IM), T<sub>max</sub> is 2–3 hours (oral/IM). Its effects last 4–6 hours but may persist for as long as 12 hours following oral dosing.

The British National Formulary recommended dose for short-term sedation is 25–50 mg orally or 25–50 mg IM, not exceeding 100 mg per IM dose when used for treatment of allergic reactions; there is no recommended maximum daily dose for sedation (Joint Formulary Committee, 2017). Total doses of up to 150 mg daily are sometimes used in acute psychiatric settings; there is evidence from toxicology studies suggesting that the lethal dose of promethazine in adults far exceeds these limits (NLM Toxnet, 2018).

In spite of its sedative properties, no studies have evaluated the use of oral or IM promethazine as monotherapy in RT. That being said, IM promethazine 50 mg has been described as a useful sedative option in benzodiazepine-tolerant patients, recommending that response should be assessed 1–2 hours after injection (Taylor et al., 2015). IM promethazine plus IM haloperidol is considered as an option for RT (NICE, 2015b) following evidence from a Cochrane review (Huf et al., 2009) of the four TREC trials, all of which included IM promethazine 25–50 mg plus IM haloperidol 5–10 mg (see Box 1 and Table 4). A more recent Cochrane review (Huf et al., 2016), included two further RCTs and concluded that IM haloperidol plus IM promethazine is effective and safe (see Intramuscular antipsychotics in combination with other medications, above).

Promethazine has no absolute contra-indication in adults (Joint Formulary Committee, 2017). Its adverse effects include drowsiness, agitation, confusion, dizziness, hypotension, central nervous system depression and lowering of seizure threshold (Burst, 1996: 99–125). It can also

cause anticholinergic effects, EPS including tardive dyskinesia, and rarely also NMS (Chan-Tack, 1999), blood dyscrasias and allergic reactions (Sanofi, 2016). In a case series ( $n = 199$ ) with 237 presentations of promethazine poisonings, the median dose ingested was 625 mg (350–1250 mg), with delirium (44%) and tachycardia (56%) the most common effects, with 10 cases admitted to the intensive care unit (Page et al., 2009). Of the 354 cases of promethazine abuse or intentional misuse reported to United States (US) Poison Centers between 2002 and 2012, the most common clinical effects were drowsiness (43.2%), agitation (13.7%), confusion (13.7%) and tachycardia (7.4%) and less than 20% required hospital admission (Tsay et al., 2015). There is no reversing agent.

### *Loxapine*

Loxapine is a dibenzoxazepine tricyclic antipsychotic with some structural similarities to clozapine (Popovic et al., 2015). The pharmacodynamic properties include receptor binding particularly at D2 and 5HT<sub>2A</sub> receptor, and a high 5HT/D2 ratio (Buckley, 1999; Glazer, 1999; Stahl, 1999). Regarding affinity for other receptors, loxapine also binds to D<sub>4</sub>, 5HT<sub>6</sub> and 5HT<sub>7</sub> receptors (Chakrabarti et al., 2007; Roth et al., 1995; Stahl, 2013) and has antagonistic properties at noradrenergic, histaminergic H<sub>1</sub> and muscarinic M<sub>1</sub> receptors (Popovic et al., 2015). This FGA has oral and short-acting IM formulations as well as a more recent inhalatory formulation but, in the UK, only the latter is available (Galen Ltd, 2018).

The oral formulation was primarily used in schizophrenia (Chakrabarti et al., 2007) and was available in the UK in the 1990s but its use was uncommon. Since the 1970s, loxapine has been evaluated for the treatment of acute disturbance. Five small-scale, randomised, double-blind trials demonstrated comparable effects on acute disturbance for oral loxapine in comparison with oral trifluoperazine (Moyano, 1975) and oral haloperidol (Selman et al., 1976) and for IM loxapine versus IM haloperidol (Fruensgaard et al., 1977; Paprocki and Versiani, 1977; Tuason, 1986).

In 2012, the US Food and Drug Administration approved an inhalatory formulation of loxapine for adults with acute disturbance associated with schizophrenia or bipolar I disorder. In the UK, the inhalatory loxapine dose is 9.1 mg. Oral inhaled loxapine has high bioavailability and T<sub>max</sub> is 2 minutes. In a phase II trial, Allen et al. (2011) evaluated inhaled loxapine in 129 acutely disturbed participants with schizophrenia or schizoaffective disorder, who were randomised to 5 or 10 mg of inhaled loxapine compared with placebo. Inhaled loxapine 10 mg showed a rapid onset of action with improvement after 20 minutes compared with placebo ( $p < 0.05$ ; secondary outcome); statistically significant differences were also

found for the 10 mg dose with respect to the PANSS-EC score compared with placebo after 120 minutes ( $p < 0.01$ ; primary outcome). In the first phase III trial, Lessem et al. (2011) found that 5 mg and 10 mg doses of inhaled loxapine were effective in reducing acute disturbance as measured by PANSS-EC in schizophrenia when compared with placebo during a 2-hour observation timeframe (both  $p < 0.001$ ; primary outcome,  $n = 344$ ). The inhaled loxapine doses of 5 mg and 10 mg were rapidly effective in reducing PANSS-EC scores even after 10 minutes (both  $p < 0.001$ ), the earliest assessment time in this trial. In the subsequent phase III trial, inhaled loxapine (5 mg and 10 mg) significantly reduced PANSS-EC scores in agitated participants with bipolar disorder compared with placebo after 10 minutes (secondary outcome;  $p < 0.0001$  for both doses), and after 120 minutes (primary outcome;  $p < 0.0001$  for both doses;  $n = 314$ ) (Kwentus et al., 2012). The use of inhaled loxapine presumes a degree of patient collaboration. This may be true for most cases of mild-to-moderate agitation, but perhaps not for more severe acute disturbance (de Berardis et al., 2017).

Concerns have been raised due to respiratory effects after loxapine inhalation and its use is contraindicated in patients with acute respiratory distress or with active airways disease such as asthma or chronic obstructive pulmonary disease (Nordstrom and Allen, 2013; Popovic et al., 2015). A brief respiratory assessment and close-proximity availability of short-acting  $\beta$ -agonist bronchodilator is recommended (de Berardis et al., 2017; Gross et al., 2014). The most common adverse effects in the three trials were dysgeusia (metallic taste), throat irritation and sedation (Allen et al., 2011; Kwentus et al., 2012; Lessem et al., 2011) and the reported severe adverse effects included two acute dystonic reactions (Allen et al., 2011; Lessem et al., 2011), two episodes of severe sedation (Kwentus et al., 2012; Lessem et al., 2011) and one episode of moderate akathisia (Kwentus et al., 2012).

### *Levomepromazine*

Levomepromazine, also known as methotrimeprazine, is an antipsychotic with pharmacology similar to the phenothiazine chlorpromazine and its antihistamine derivative promethazine. Levomepromazine is more sedating than chlorpromazine and, additionally, it has antiemetic, antihistamine and anti-adrenaline activity. It is available as oral tablets and as a solution for IM and IV injection and subcutaneous infusion (Sanofi, 2017; Wockhardt UK Ltd, 2017). T<sub>max</sub> is 1–3 hours for the oral route (bioavailability 50–60%) and 30–90 minutes for the IM route. Its common side-effects include QT prolongation and hypotension (Wockhardt UK Ltd, 2017).

The oral formulation is licensed as an alternative to chlorpromazine in the treatment of schizophrenia (Sanofi, 2017), although a Cochrane review, which included four



RCTs, was not able to confidently comment on the effectiveness of levomepromazine for schizophrenia (Sivaraman et al., 2010). However, it is commonly used parenterally in the management of terminal illness for its profound sedative and antiemetic properties; it is frequently administered in combination with other central nervous system agents or analgesics (e.g. opiates) via a syringe driver.

Published studies for its use in the management of acute disturbance are sparse, with no published evidence for the efficacy of oral levomepromazine monotherapy in the management of acute disturbance pre-RT. A small randomised open trial ( $n = 19$ ) comparing oral haloperidol versus oral haloperidol plus oral levomepromazine found no clear difference between groups (Higashima et al., 2004). Bucci and Saunders (1964) studied the effect of IM levomepromazine (dose range 25–100 mg) in 35 female patients over timeframes that are not relevant to RT (days or weeks). Of concern, 14 of the 35 patients demonstrated apathy and psychomotor depression further into the study.

More recently, a Japanese open-label, flexible-dose, naturalistic observational study (Suzuki et al., 2014) for the treatment of acute disturbance in inpatients ( $n = 122$ ) with schizophrenia, compared the efficacy and safety of IM olanzapine, IM haloperidol and IM levomepromazine ( $n = 37$ ). Notably, the participants in this study were receiving concomitant additional antipsychotic treatment. Clinical symptoms and safety were assessed using standard scales at 1 hour after IM medication. The results display a varied picture in that mean changes from baseline for PANSS-EC, ACES, Barnes Akathisia Rating Scale (BARS; Barnes, 1989), Abnormal Involuntary Movement Scale (Guy, 1976a), and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS; Inada, 1996) were significantly better for IM levomepromazine and IM olanzapine, as compared with IM haloperidol. Within these, the mean changes from baseline for BARS and DIEPSS were significantly better for IM olanzapine versus IM levomepromazine. Furthermore, the mean change from baseline for the PANSS positive subscale was much better for IM olanzapine and IM haloperidol, as compared with IM levomepromazine. They concluded that the effects of IM olanzapine and IM levomepromazine on acute disturbance are more rapid than those of IM haloperidol, but also suggest that compared with IM levomepromazine, IM olanzapine is safer and affords greater improvement in symptoms.

Although the published evidence is lacking, the potential safety concerns referred to by these two studies (Higashima et al., 2004, Suzuki et al., 2014) are also highlighted in the recent Cochrane review on levomepromazine, which was for the different clinical setting of palliative care. This review commented that the higher doses used to achieve antipsychotic activity are more likely than lower doses to cause significant sedation or postural hypotension (Cox et al., 2015).

### *Zuclopenthixol acetate*

Zuclopenthixol acetate (ZA) is an FGA and is best known by its trade name Clopixol Acuphase®. Zuclopenthixol is a thioxanthine dopamine antagonist first introduced in the early 1960s. Its elimination half-life is around 20 hours. IM injection of zuclopenthixol base results in rapid absorption and a duration of action of 12–24 hours. By slow absorption after IM injection, the effective half-life (and so duration of action) becomes dependent on the rate of release from the IM reservoir. This can be achieved by esterification of the zuclopenthixol molecule; the rate of release being broadly proportion to the length of the ester carbon chain. Thus, zuclopenthixol decanoate is slow to act but very long-acting as a result of retarded release after IM injection. Alternatively, ZA is administered intramuscularly and it provides relatively prompt release but with an intermediate duration of action.

The initial pharmacokinetic study of ZA included 19 participants 'in whom calming effect by parenteral neuroleptic was considered necessary' (Amdisen et al., 1986). Zuclopenthixol was detectable in the plasma after 1–2 hours but did not reach peak concentrations until around 36 hours after dosing. At 72 hours, plasma concentrations were around a third of those at 36 hours. The clinical effect of ZA was not rapid as 10 of 17 participants exhibited minimal or no change in psychotic symptoms at 4 hours. Sedation was evident at 4 hours but it had effectively abated by 72 hours.

A follow-up study by the same research group examined more closely the clinical effects of ZA in 83 participants (Amdisen et al., 1987). The authors concluded that ZA produced 'pronounced and rapid reduction in psychotic symptoms'. In fact, psychotic symptoms were first assessed only after 24 hours and so a claim of rapid effect is not reasonably supported. Sedative effects were measured (0 = no sign of sedation; 1 = slightly sedated; 2 = moderately sedated) after 2 hours when a statistically significant effect was observed. Mean sedation scores were 0.0 at baseline, 0.6 at 2 hours, 2.2 at 8 hours and 1.1 at 72 hours. Dystonia and rigidity were the most commonly reported adverse effects.

Two independently conducted open studies produced similar results with a slow onset of effect peaking at 24 hours and still being evident at 72 hours (Balant et al., 1989; Lowert et al., 1989). Thereafter, the first UK study reported that a significant reduction in psychosis score was first evident at 8 hours and scores continued to fall until the last measurement at 72 hours; of 25 participants assessed only four showed signs of tranquillisation at 1 hour, 19 participants at 2 hours and 22 participants at 24 hours (Chakravarti et al., 1990).

The first comparative trial of ZA examined its effects and those of IM/oral haloperidol and IM/oral zuclopenthixol.



thixol in multiple doses over 6 days (Baastrup et al., 1993). The two non-ester, IM/oral preparations produced a greater degree of sedation at 2 hours than did ZA, but the effect of ZA and zuclopenthixol was more sustained than with haloperidol over 144 hours (although participants received more zuclopenthixol doses). No clear differences between treatments were detected, with the exception of the slow onset of effect of ZA. The number of doses given varied substantially: ZA 1–4; haloperidol 1–26 and zuclopenthixol 1–22. The key, and perhaps unique, advantage of ZA is that it reduces the need for repeat doses in acute psychosis. Indeed, this was the principal finding of the first double-blind study of ZA (Chin et al., 1998). Participants were given either ZA or IM haloperidol and assessed over three days. Changes in BPRS and Clinical Global Impression (CGI) (Guy, 1976b) scores were near identical on each daily assessment. However, only 1 of 23 ZA participants required a second injection whereas 7 of 21 required a repeat dose of haloperidol. Rapidity of onset was not examined. Similar findings were reported by Thai researchers comparing the same treatments (Taymeeyapradit and Kuasirikul, 2002) and in three other studies of moderate size (Al-Haddad et al., 1996:  $n = 49$ ; Brook et al., 1998:  $n = 44$ ; Chouinard et al., 1994:  $n = 40$ ). In each study, the timing of assessments was such that time to onset of effect could not be determined.

A Cochrane review by Jayakody et al. (2012) included all of the above comparative studies as well as three further studies (Liu et al., 1997; Ropert et al., 1988; Uys and Berk, 1996) for which we were unable to obtain full details. The authors concluded that all studies were methodologically flawed and poorly reported and that ZA did not appear to have a ‘rapid onset of action’. They noted that ZA was probably no less effective than other treatments and that its use might ‘result in less numerous coercive injections’.

Overall, the utility of ZA in RT is limited by a somewhat delayed onset of both sedative and antipsychotic actions. Sedation may be apparent in a minority of patients after 2–4 hours, but antipsychotic action is evident only after 8 hours. If ZA is given to a restrained patient, their behaviour on release from restraint is likely to be unchanged and will remain as such for several hours. ZA has a role in reducing the number of restraints for IM injection but it has no role in RT. Further, as new indications are considered such as agitation due to novel psychoactive substances (NPS), there is as yet no evidence to support the use of ZA in RT, even when BNF dose limits have been exhausted for other more commonly used drugs in RT. An ECG is advised (Joint Formulary Committee, 2018).

#### *Dexmedetomidine*

IV dexmedetomidine is a highly selective  $\alpha_2$ -adrenergic

receptor agonist that is used in general hospitals, particularly so in medical and surgical intensive care units (Maze et al., 2001). In a meta-analysis of 14 RCTs including a total of 3029 participants in an intensive care unit setting, IV dexmedetomidine appeared to be superior to all other agents, including midazolam and placebo, showing a significant reduction in the incidence of agitation, confusion and delirium (Pasin et al., 2014). Calver and Isbister (2012) investigated the effectiveness and safety of IV dexmedetomidine in difficult-to-sedate patients (i.e. when two attempts at parenteral sedation failed) and reported that it was successful in achieving sedation in all but one patient, although the effect was short lasting and adverse events were frequent, mostly hypotension. The authors concluded that safe administration of dexmedetomidine is beyond the monitoring capability of most emergency departments. Although dexmedetomidine is an established option in the medical intensive care unit, there is scant evidence for its use in the emergency department.

#### *Barbiturates*

Until around 20 years ago, barbiturates such as IM amylobarbitone were sometimes used in RT (Pilowsky et al., 1992). Barbiturate use was unsupported by any formal trials or publications. Moreover, as potent respiratory depressants for which no reversing agent is available, barbiturates are exceptionally dangerous drugs when given parenterally and facilities for mechanical ventilation should be available (Kerr and Taylor, 1997; Taylor et al., 1999). Today, only barbiturates used in anaesthesia remain licensed and readily available. Amylobarbitone is available on a ‘named-patient’ basis but it cannot be recommended for RT given the dangers associated with its use and the near absence of experience of its use amongst clinicians working in acute psychiatry in the context of RT.

#### *Valproate*

Sodium valproate was originally introduced as an antiepileptic agent in the 1960s and, soon after, there were reports of its use in bipolar disorder. There have been suggestions that it is of use in acute disturbance, in the context of varying diagnoses, since 1988 (Haddad et al., 2009). It is not generally included in RT protocols but has an acknowledged role in the optimisation of management in patients who are experiencing mania (Bowden et al., 1994; Freeman et al., 1992; Goodwin et al., 2016). In the absence of affective symptoms, there is limited evidence and a lack of RCT evidence to support the role that valproate may have in the management of aggression (Lindenmayer and Kotsaftis, 2000).

In schizophrenia, some uncontrolled studies have suggested that there may be promise for oral valproate as an

anti-aggressive agent (Chong et al., 1998; Citrome et al., 2004) but this has not been established in later controlled studies (Volavka and Citrome, 2008). In a Cochrane review, its use as adjunct treatment in the management of schizophrenia in the absence of aggressive symptoms was concluded to have a limited evidence base (Wang et al., 2016).

The best evidence regarding oral valproate is in managing mania which, arguably, could reduce the requirement for RT. In placebo-controlled trials, valproate was found to be effective and comparable to lithium (Bowden, 2003; Pope et al., 1991). However, there is evidence to suggest that the combination of an SGA with sodium valproate is more effective (Goodwin et al., 2016; Ogawa et al., 2014). It should be stressed that these would be treatment choices to stabilise manic symptoms over a period of days rather than in clinical situations where RT is to be considered. Although Keck and McElroy described a rapid clinical response after using 'loading' doses of valproate for a small number of patients (Keck et al., 1993; McElroy et al., 1993, 1996), larger trials are needed.

The limited evidence for the use of valproate in aggression should be considered in the context of the potential side effects although weight gain, which is the most problematic, would not necessarily be considered in the acute situation. However, all prescribers must be aware that it should not be prescribed to women of child-bearing age due to the risk of teratogenicity (NICE, 2016a).

### *Ketamine*

Ketamine is an NMDA receptor antagonist that is used as an anaesthetic agent, particularly in emergency situations. In recent years there has been a large amount of research into the use of IV ketamine infusions (most commonly at a dose of 0.5 mg/kg) as a rapidly acting antidepressant treatment (Berman et al., 2000; Zarate et al., 2006). There have been reports that in addition to being an antidepressant, ketamine has a specific acute anti-suicidal effect (Wilkinson et al., 2017). Such effects may be of relevance to the management of the mental disorder underlying the acute disturbance. However, the use of IV ketamine is complicated. In a psychiatric context, it is usually recommended for use administered by an anaesthetist in an electroconvulsive therapy (ECT) suite, which ensures full resuscitation equipment is to hand (Diamond et al., 2014).

In terms of the specific use of ketamine for the management of acute disturbance, this has mostly been investigated in emergency departments where there is extensive evidence regarding its use for procedural sedation (Bellolio et al., 2016) and the management of pain (Motov et al., 2017). It is argued to be an ideal medication to sedate patients, with a rapid onset of action and minimal effects on airway control, breathing, heart rate, or blood pressure

(Scaggs et al., 2016). Data from emergency departments are sparse but include a small retrospective review of 27 patients treated with IM ketamine. This found few major adverse effects on vital signs (mean systolic blood pressure increase of  $17 \pm 25$  mm Hg and increased heart rate of  $8 \pm 17$  beats/min), even in a population with alcohol or drug intoxication in 40.6% (Hopper et al., 2015). However, 62.5% of patients required additional pharmacologic treatment for agitation. A subgroup analysis of a blinded RCT that compared IM droperidol, IM midazolam and their combination (Calver et al., 2015b; Isbister et al., 2010) considered a group of 49 patients for whom droperidol failed to induce adequate sedation and who were subsequently administered IM ketamine of varying doses (4–6 mg/kg) (Isbister et al., 2016). With no serious adverse events reported, ketamine was found to be effective when administered in doses  $> 200$  mg.

A more recent prospective observational non-randomised study compared ketamine (IM 4–6 mg/kg or IV 1–2 mg/kg) with IM haloperidol, IM/IV midazolam, IM/IV lorazepam, and the combination of an IM/IV benzodiazepine plus IM haloperidol for acute disturbance in around 100 participants (Riddell et al., 2017). Ketamine led to significantly less agitation at 5, 10 and 15 minutes compared with the other treatments and there was no difference in the need for re-dosing or adverse effects between treatments, but the treatment group sizes were small ( $n = 10$ –33).

There have also been several reports of the use of ketamine in 'pre-hospital' settings by paramedics and emergency medical staff; its rapid onset of action being its main advantage (Burnett et al., 2015). For example, a retrospective case series of seven young patients (mean age 24 years) with 'excited delirium' were reported to have been successfully and safely treated with IM ketamine (mean dose 4.4 mg/kg) (Scaggs et al., 2016). A larger retrospective study of 52 patients treated with IM ketamine 4 mg/kg also found a high rate of rapid sedation (in 50/52 patients) (Scheppke et al., 2014). In this study, 26 patients were also given IM/IV midazolam to prevent emergence reactions with ketamine. Of these, three patients experienced significant respiratory depression with two needing intubation. Higher rates of intubation (23%) were also reported in another retrospective review of 36 patients treated with IM or IV ketamine (Keseg et al., 2015). A prospective open-label study of IM ketamine (5 mg/kg) versus IM haloperidol (10 mg) in 146 subjects found the median time to 'adequate sedation' was significantly shorter with IM ketamine (5 vs 17 mins) (Cole et al., 2016). However, complications occurred in 49% of patients treated with IM ketamine (hypersalivation, vomiting, laryngospasm) versus 5% treated with haloperidol and, again, significantly more patients treated with ketamine required intubation (39% vs 4% of those treated

with haloperidol). Use of ketamine is supported by the Royal College of Emergency Medicine, but without comment on the strength of evidence (Gillings et al., 2016).

Intranasal esketamine, the active stereoisomer of ketamine, is being investigated by the pharmaceutical industry as a potential treatment for depression, and intranasal administration of ketamine has been proposed for the treatment of patients with severe acute disturbance in the emergency department (Normandin et al., 2016). This may be a safer and easier method of administration. However, more research is required to examine this approach. Pending this, IM or IV ketamine is likely to be relatively rarely used for RT. Importantly, it should be recognised that it leads to sedation rather than tranquillisation and availability of resuscitation equipment is required.

#### *Electroconvulsive therapy (ECT)*

Royal College of Psychiatrists (2013) guidance states that ECT is not a desirable measure to treat the risk of violence and NICE (2015b) guidelines on managing acute disturbance do not mention ECT. That being said, ECT may be a consideration for cases with prolonged and severe behavioural disturbance associated with certain psychiatric disorders. In such scenarios it is not inconceivable that RT may have been repeatedly utilised as a management strategy.

ECT reduces disturbed behaviour in mania by treating the manic episode. Although NICE guidelines on the management of bipolar disorder do not mention ECT for mania (NICE, 2016b), NICE guidelines on the use of ECT recommends it for prolonged or severe manic episodes but only to achieve rapid and short-term improvement after other treatments have failed or when the condition is life threatening (NICE, 2009). WFSBP guidelines for the treatment of bipolar disorder recommend ECT for acute manic episodes that are resistant to pharmacotherapy (Grunze et al., 2010), whereas BAP guidelines reserve ECT for patients with mania who are severely ill, whose mania is treatment resistant (including mixed states) and who express a preference for ECT (Goodwin et al., 2016). Others suggest that ECT may be considered at any point in the treatment of acute mania if the patient has a history of positive response or is intolerant of medications (Mohammad and Osser, 2014).

Reviews attest to the efficacy of ECT in treating mania (Mukherjee et al., 1994), with some also citing the speed of treatment effect. ECT may reduce catatonia, aggression and excitement (Fink, 2001). In a review of the use of ECT in patients with catatonia, Luchini et al. (2015) highlighted that ECT is 80–100% effective in all forms of catatonia, including delirious mania or severe catatonic excitement, even after pharmacotherapy has failed.

ECT has also been found to be effective in augmenting

antipsychotic treatment in treatment-resistant schizophrenia (Lally et al., 2016; Petrides et al., 2015). In a review of 31 articles on the indications for ECT in schizophrenia, Pompili et al. (2013) concluded that ECT in combination with pharmacotherapy is recommended for patients with schizophrenia presenting with catatonia, aggression or suicidal behaviour, when rapid global improvement and reduction of acute symptomatology are required. In a retrospective study of 20 hospitalised patients with schizophrenia or schizoaffective disorder who had received ECT treatment, aggression was found to be significantly reduced (Iancu et al., 2015). Kristensen et al. (2012) reviewed the medical records of eight forensic inpatients with schizophrenia, whose psychotic symptoms were accompanied by seriously assaultive behaviour and were unresponsive to medication; all but one had an excellent or good symptomatic and behavioural response to ECT.

#### *From evidence to practice*

**Recommended.** Although no studies have evaluated the use of oral or IM formulations of promethazine as monotherapy, there is good evidence supporting its IM use in combination with haloperidol and so promethazine may also be effective as monotherapy. Oral-inhaled loxapine has trial evidence of efficacy supporting its use 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.

**Not recommended.** Oral levomepromazine, valproate and barbiturates have a lack of evidence for use in RT. Although IM levomepromazine has some evidence of effectiveness, this has to be weighed against the risk of cardiovascular adverse effects, especially hypotension. IM ketamine has some evidence of effectiveness, but it carries an important risk of respiratory depression and does not have a reversing agent. IV dexmedetomidine has good evidence of effectiveness but is not safe for use in settings other than possibly in medical intensive care units.

**For consideration for non-response.** ZA is not recommended for use as RT as the evidence does not support it, particularly as its onset of action takes several hours. However, after other strategies have failed to achieve a required response, its use may be considered as this may result in less numerous injections. A baseline ECG is advised before use due to the risk of QTc prolongation.

ECT may also be considered when other strategies have failed to achieve a required response, and particularly if the underlying disorder has an evidence base for the use of ECT (e.g. mania) or if there is a history of good response for the individual patient.

## Modifiers, special settings and circumstances

### *Pregnancy*

Women with pre-existing mental illness are at risk of relapse during pregnancy (NICE, 2014c) and may require hospitalisation, which in turn may include the management of acute disturbance. Commonly, medicines would be avoided during pregnancy; however, this is not always possible, in which case many treatment guidelines recommend treating the mother as per usual clinical algorithms (NICE, 2014c, 2015b).

Pharmacological and pharmacokinetic changes in pregnancy affect drug handling, including: variations in clearance between trimesters; increased glomerular filtration rate; and expansion of plasma volume, which subsequently return to pre-pregnancy states soon after delivery (Wesseloo et al., 2017). Avoiding drugs that may accumulate in both maternal and foetal tissues is an advisable precautionary measure, as is selecting medication with a short half-life (McAllister-Williams et al., 2017).

There are risks to the foetus associated with the use of medicines during pregnancy, but there are also risks to the foetus or neonate if the mother's mental illness were to relapse as a consequence of no treatment. The main concern when prescribing medication for pregnant mothers is whether the medication may increase the baseline risk of malformations in the embryo, affect foetal development or lead to complications at birth. Exposure to a teratogen in the first trimester is more likely to cause structural malformations, whereas later exposure is more likely to cause growth defects (McElhatton, 2010). The risk of teratogenicity may be increased if the number of concomitant drugs is increased (UKMi, 2014). Teratogenic risk can differ among individuals and not every foetus will be affected (McElhatton, 2010). During the second and third trimesters, organs such as the cerebral cortex and the renal glomeruli continue to develop and remain particularly susceptible to damage. Teratogenic effects are usually dose dependent and the dose response curve is steep, in that a small increment in dose can result in a large increase in foetal toxicity (McElhatton, 2010). Due to late-stage pregnancy in utero exposure, benzodiazepines can lead to floppy baby syndrome and antipsychotics are associated with EPS in the neonate.

In a retrospective case series ( $n = 80$ ), 39% of pregnant women received oral or IM medication for acute disturbance in a US emergency department; the authors did not make any active recommendations as to what to use (Ladavac et al., 2007). Existing RT guidelines give only general advice about the principles of management during pregnancy and do not provide a bespoke RT algorithm for use in pregnancy (McAllister-Williams et al., 2017; NICE, 2014c, 2015b). This is presumably due to the lack of RCTs conducted in pregnancy resulting from both feasibility

and ethical concerns, and because the numbers involved in many studies are too small to allow for specific evidence-based recommendations. Consequently, we highlight here the importance of reporting the outcomes of pregnancies exposed to medication to the UK Teratology Information Service (UKTIS; <http://www.uktis.org/>).

The Maudsley Prescribing Guidelines (Taylor et al., 2015) highlight the lack of published information on the use of RT in pregnant women, and state that acute use of short-acting benzodiazepines such as lorazepam and of the sedative antihistamine promethazine is unlikely to be harmful; there is a caveat presumption that the use of either would be problematic immediately before birth. Recent WFSBP guidelines (Garriga et al., 2016) echo the lack of evidence in management of acute disturbance in pregnancy and suggest that verbal interventions should be employed whenever possible; followed by the minimally effective dose of medication, if necessary. NICE guidelines on the general treatment of psychiatric disorders in pregnancy (NICE, 2014c), recommends that benzodiazepines are not offered to pregnant women, except for the short-term treatment of anxiety and agitation, and that antipsychotic choice considers that there is limited data on safety in pregnancy. It also states that when choosing RT medication, an antipsychotic or benzodiazepine with a short half-life should be considered; it does not specify a particular drug. The BAP Consensus Guidelines (McAllister-Williams et al., 2017) endorse this point and add that, in RT, the minimum effective dose should be used for antipsychotics due to the risk of EPS and that for benzodiazepines, the risks of floppy baby syndrome should be taken into account.

UKTIS collects pregnancy outcome data from women who have been exposed to drugs and chemicals in pregnancy. It does not currently have any specific information in relation to lorazepam or any other benzodiazepine. In relation to haloperidol, UKTIS states that the published data do not demonstrate any increased risk of congenital malformations or spontaneous abortion following haloperidol exposure in pregnancy (UKTIS, 2014). For promethazine, UKTIS states that two small studies on foetal exposure to promethazine by maternal overdose do not suggest an association between in utero promethazine exposure and increased risks of congenital malformation, pre-term delivery, low birth weight or adverse neurodevelopmental outcome; risk of spontaneous abortion has not been studied. In the UK, manufacturers of promethazine state that, due to the risk of neonatal irritability and excitement, use should be avoided in the last two weeks of pregnancy (UKTIS, 2014). Recent meta-analyses (Magee et al., 2002), Cochrane reviews (Boelig et al., 2016; Matthews et al., 2015) and guidelines (NICE, 2008; RCOG, 2016) have concluded that promethazine is safe to use in pregnancy in the ongoing management of nausea and



hyperemesis gravidarum and recommend it; although this does not confirm its efficacy for RT in pregnancy, it does provide a degree of evidence regarding its safety.

Due to the lack of an evidence base for pregnant women, RT decisions are potentially more challenging when non-parenteral options (pre-RT) have been exhausted. For IM promethazine (Sanofi, 2016), IM lorazepam (Pfizer, 2014) and IM haloperidol (Concordia, 2017) there is no contraindication in pregnancy stipulated by the European licence for each drug respectively.

The relative risks of using one medicine over another in pregnancy versus leaving the patient untreated are difficult to assess due to a paucity of evidence and due to confounders such as concurrent medication, lifestyle and the illness itself. However, such concerns may be more relevant in relation to ongoing use of medication, not single doses as administered for RT. The direct effects of RT on the embryo or foetus are likely to be minimal, but the risks associated with use of restraint and ongoing regular medicines are likely to be more significant to the embryo or foetus; these should inform prescribers' plans for short-term management such as RT. Further considerations such as restraint positions (not prone or supine but semi-seated), techniques and equipment (e.g. use of beanbags) and suitable injection sites (gluteal or lateral thigh) are beyond the scope of this review but are addressed elsewhere (McAllister et al., 2017; NICE, 2015b).

#### *Intoxication and withdrawal*

There is little specific evidence about management of acute disturbance requiring RT where substance use is implicated. Clinical experience constitutes the available evidence. The use of drugs and alcohol and their relationship to mental disorders is outside the scope of this guideline; for their management, please see BAP guidelines on addiction (Lingford-Hughes et al., 2012). NG10 recognises that there are 'major problems' in managing substance-related violence with some patients inappropriately transferred to police cells (NICE, 2015b). In general, studies do not stipulate which substances are implicated, although alcohol, synthetic cannabinoids, gammahydroxybutyrate (GHB) and stimulants are most likely to be associated with acute disturbance.

One of the TREC trials examined the impact of substance misuse and found that IM midazolam or IM haloperidol plus IM promethazine were both effective and 'reasonably safe' (see Box 1 and Table 4) (TREC Collaborative Group, 2003). In other clinical guidelines, benzodiazepines are generally recommended due to their limited side-effect profile and propensity for drug interactions, the ability to titrate and to reverse their effects with flumazenil, particularly in an acutely disturbed patient where there is uncertainty about diagnosis and other drugs taken (Lingford-Hughes et al., 2012; NICE, 2015b). It is less clear what the best

alternative is for those who may be benzodiazepine tolerant or dependent, alcohol dependent or have taken other respiratory depressants, although benzodiazepines are still likely to be the best approach with monitoring. Concerning antipsychotics, the risk of lowering seizure threshold and impact on cardiovascular rhythm means they should be used with caution and monitoring. In addition, the use of antipsychotics may complicate diagnosis of a psychotic presentation regarding whether it is 'drug induced' on a background of a psychotic illness. Once the acute presentation has resolved, a 'brief intervention' about the link between drug use and consequences should be delivered, as well as consideration given to referral to addiction services for more support and specialised treatment.

Management of alcohol withdrawal and its complications are covered in two NICE guidelines: CG100 (NICE, 2010) and CG115 (NICE, 2011). Benzodiazepines are generally preferred and for delirium tremens, parenteral lorazepam or haloperidol is recommended. Wernicke's encephalopathy and risk of thiamine deficiency should be considered and treated with parenteral thiamine (Lingford-Hughes et al., 2012; NICE, 2010, 2011).

For many of the novel psychoactive substances (NPS), rapid urine or field tests are not available, so assessment is critical for the diagnosis to be made. Clinicians should know signs and symptoms of intoxication and withdrawal of such substances, which broadly fall into the following groups: stimulants, depressants and hallucinogens. The Novel Psychoactive Treatment UK Network guidelines and website (<http://neptune-clinical-guidance.co.uk/>) are excellent resources regarding NPS and the associated clinical presentations and management of acute harms, including acute disturbance (Abdulrahim et al., 2015). Advice on acute clinical management is also available from the National Poisons Information Service (<https://www.toxbase.org/>). Cases of suspected harm from illicit substances, including NPS, can be reported to Public Health England (<https://report-illicit-drug-reaction.phe.gov.uk/>).

Gammahydroxybutyrate (GHB) withdrawal can be associated with acute disturbance and is a potentially life-threatening condition that should therefore be considered as a medical emergency (Abdulrahim et al., 2015). Substantial doses of diazepam and/or admission to the medical intensive care unit with intubation to manage the acute disturbance have been described. GABA-B receptors are a target for GHB and addition of baclofen 10 mg three times a day to benzodiazepines has been reported to improve symptom control and reduce the need for large benzodiazepine doses (Lingford-Hughes et al., 2012).

#### *Rapid tranquillisation in the general hospital*

The emergency department of a general hospital is a clinical environment that affords the safe administration of a wider range of interventions and formulations than is possible in a

psychiatric inpatient setting. With ready access to resuscitation equipment and ventilation apparatus, the risk versus benefit considerations can be different; this is especially pertinent when standard options and preparations fail. IV medications can be used, but these should be considered in line with the evidence outlined above.

As a general hospital has different clinical settings, there is a variety of scope for advanced medical risk management. For example, the emergency department is different to the medical intensive care unit in the general hospital; the latter being outside the scope of our guideline. In addition to the inpatient psychiatric setting, our guideline is also relevant to the standard general hospital acute setting with its ready access to resuscitation equipment and ventilation apparatus.

#### *Psychiatric intensive care units and inpatient forensic psychiatric settings*

PICUs are for patients who are in an acutely disturbed phase of a serious mental disorder (NAPICU, 2014). There is an associated loss of capacity for self-control, with a corresponding increase in risk, which does not allow for their safe, therapeutic management and treatment in a less secure ward. PICUs utilise a range of restrictive interventions including seclusion. Forensic psychiatric settings may also use highly restrictive interventions such as segregation or mechanical restraint. These are specialist interventions that require an enhanced understanding of how restrictive interventions can be safely and effectively used individually and in combination.

Inpatient forensic psychiatric settings are for patients who suffer from a mental disorder and who have carried out, or are at increased risk of, serious violence to others and may have been in contact with the Criminal Justice System. They provide acute treatment and rehabilitation within relevant levels of security, with an emphasis on interventions to reduce the risk of recidivism and violence associated with mental disorder.

In principle, the interventions used to manage acute disturbance in such patients should not differ from those described in this guideline. That said, the harmful effect of inadequately managed acute disturbance in PICU and inpatient forensic settings is likely to be more severe in both nature and degree than that seen in general acute wards. The patient population in these settings often has a history of past trauma (Briere et al., 2016), which can lead to the triggering of extreme responses to restrictive interventions, such as parenteral medication and physical restraint. Trauma-informed care management is recommended (Muskett, 2014). Polypharmacy and high-dose antipsychotic prescribing is more common in forensic settings and hence the additional prescribing of RT requires due caution and attention to the risk of adverse effects (Stone-Brown et al., 2016).

#### *Seclusion*

The efficacy of seclusion as an intervention used to manage acute disturbance in its own right is outside the scope of this guideline. Here we will briefly consider the relationship between RT and the act of seclusion. A patient in seclusion should have access to a range of interventions to manage acute disturbance.

In the case of RT and seclusion, one may precede the other, or they may be used concurrently. Data are largely unavailable regarding concurrent use. A survey of a medium secure forensic service found that 10% of patients were concurrently secluded and given RT (Haw et al., 2013) and in a general psychiatric sample this was found to be the case for 40% (Talukdar and Lekka, 2013). It is important to note that although these percentages are probably not generalisable, they are not small. In an RCT where participants were randomly allocated to seclusion or RT as first intervention, more than a third of participants eventually experienced both interventions (Georgieva et al., 2012).

Patients receiving RT who are subsequently secluded, or patients in seclusion who receive RT, can present some challenges around psychiatric monitoring. The Mental Health Act Code of Practice (Department of Health, 2015) specifies that secluded patients should be under continuous psychiatric observation with regular nursing (two-hourly) and medical (four-hourly) seclusion reviews (Bhavsar et al., 2014). The schedule and nature of seclusion reviews is not the same as the intensity of physical monitoring observations recommended for RT.

#### **Physical health monitoring and RT**

The rationale for physical health monitoring is based on the risk of adverse effects of RT medication, including EPS, sedation, respiratory depression, tachycardia, QTc prolongation with associated risk of arrhythmia, postural hypotension, increased seizure potential and NMS (Innes and Curtis, 2015; Innes and Iyeke, 2012; Innes and Sethi, 2013; Loynes et al., 2012; Macpherson et al., 2005). Pre-existing physical health comorbidities, pregnancy, drug or alcohol intoxication or withdrawal and potential medication interactions confer additional risks (Loynes et al., 2012). Non-medication risks are also a factor and may include the process of restraint (Innes and Curtis, 2015; Loynes et al., 2012). Furthermore, there are the practical challenges of delivering an IM injection into the correct muscle at the correct depth (Abdelmawla and Mitchell, 2006; Blofeld et al., 2003). Consequently, post-RT physical monitoring and documentation is required (Innes and Curtis, 2015; NHS Litigation Authority, 2013; NICE, 2017).

Most mental health organisations include some policy or protocol guidance for the monitoring of physical health

**Table 6.** Summary of key guidelines on post-RT monitoring

Guideline	Post-RT parameters	Post-RT monitoring	Additional recommendations
Maudsley Prescribing Guidelines 12th edition (Taylor et al., 2015)	Temperature; pulse; blood pressure; respiratory rate	Every 10 minutes for 1 hour, then half-hourly till patient ambulatory	Poor engagement: observe for pyrexia, hypotension, over-sedation, and general physical well-being. Asleep/unconscious: continuous pulse oximetry desirable with nurse presence.
NG10 (NICE, 2015b)	Temperature; pulse; blood pressure; respiratory rate; hydration level; consciousness level; side effects	At least hourly until no further concerns or every 15 minutes (in certain circumstances)	Higher frequency if BNF maximum dose exceeded in prescribing; patient asleep or sedated; associated drugs and alcohol; pre-existing physical health concerns; experienced harm due to restrictive intervention.
NICE Quality Standard QS154 (NICE, 2017)	Vital signs; hydration level; consciousness level; side effects;	At least hourly until no further concerns	If RT is used while the person is in seclusion, additional measures may be needed to ensure safety.
Assessment and management of agitation in psychiatry: expert consensus (Garriga et al., 2016)	Vital signs	Every 15 minutes for 1 hour then every 30 minutes for 4 hours or until awake	Vigilant documented monitoring should be mandatory when physical restraint is used.

RT: rapid tranquillisation; BNF: British National Formulary

post-RT, and yet these are far from uniform (Innes and Sethi, 2013; Loynes et al., 2012). Such variations reflect inconsistency between recommendations from national and international guidelines. Indeed, in national surveys, 97% of RT documents ( $n = 44$ ) specified monitoring parameters but there was considerable variation with a range of 14 different parameters listed (Innes and Iyeke, 2012; Loynes et al., 2012).

Table 6 summarises the key points from guidelines that make pertinent recommendations; the following guidelines make no additional recommendations and are not included: American Association for Emergency Psychiatry (Wilson et al., 2012a); British Association for Psychopharmacology (Barnes et al., 2011); and Austrian Society for Neuropsychopharmacology and Biological Psychiatry (Frey et al., 2015).

In general, the recommended physical health parameters include all those that are monitored by the National Early Warning Score (NEWS) namely, temperature, pulse, systolic blood pressure, respiratory rate, oxygen saturation, level of consciousness or new confusion, as these are evidenced as good predictors of patient mortality and deteriorating health (Gao et al., 2007; Royal College of Physicians, 2017). Additionally, ECGs, hydration status and blood tests have been recommended post-RT (Macpherson et al., 2005).

There is an absence of evidence to stipulate the frequency and duration of monitoring post-RT. Most, if not all, of the evidence is based on expert committee and

consensus recommendations. The most prescriptive guidance recommends physical health monitoring every 5–10 minutes for the first hour, then every 30–60 minutes until the patient is ambulatory (Macpherson et al., 2005). A singular approach is not possible due to differing monitoring needs for a higher-risk scenario. The monitoring guidance for individual medications found in their SmPC can also direct longer durations of monitoring. For example, the SmPC recommends monitoring for at least 8 hours after parenteral lorazepam (Pfizer, 2014), and for a minimum of 4 hours post-IM olanzapine (Eli Lilly, 2017b). In general, a phased approach to monitoring is widely reported in current clinical practice, with monitoring every 15 minutes post-RT with IM medication for up to an hour, followed by a lower intensity monitoring phase (hourly up to 4 hours); the latter is subject to whether a patient is ambulatory (Innes and Iyeke, 2012).

Ultimately, physical health monitoring essentially requires direct ‘hands-on contact’ but also needs to be practically feasible and safe. There will be times when direct contact physical observations are associated with increased risks to staff and/or the patient and may even have the counterproductive effect of re-escalating a situation. Examples may involve a secluded patient or one whose degree of acute disturbance is associated with poor engagement with clinicians. For this difficult-to-monitor patient group, there is no evidence base or guidance as to what may constitute non-contact physical monitoring. Respiratory rate, level of consciousness and clinical

**Table 7.** Direct contact monitoring levels

Level	Criteria	Physical monitoring schedule	Suggested minimum psychiatric observations
<b>Low</b>	All patients following pre-RT medications	NEWS or equivalent every hour for minimum 1 hour	Standard psychiatric observations every hour
<b>Medium</b>	All patients post IM RT, who do not require high/critical level monitoring	NEWS or equivalent every 15 minutes for minimum 1 hour	Intermittent psychiatric observations every 15 minutes
<b>High</b>	All patients post IM RT, who are over-sedated, asleep, or significantly physically unwell	NEWS or equivalent every 15 minutes for minimum 1 hour and include pulse oximetry until patient is ambulatory	Continuous (within line of sight)
<b>Critical</b>	All patients post IV RT as well as patients who are unconscious (not rousable) or severely physically unwell	Continuous monitoring and resuscitation facilities are essential	Continuous (within arm's length)

IM: intramuscular; IV: intravenous; NEWS (National Early Warning Score): temperature, pulse, systolic blood pressure, respiratory rate, oxygen saturation, level of consciousness; RT: rapid tranquillisation.

observational signs (pallor, signs of pyrexia, evidence of dystonia or akathisia and signs of dehydration) have been suggested as practical for such scenarios until direct contact physical monitoring can be established (Innes and Iyke, 2012; Loynes et al., 2012; Macpherson et al., 2005). As technology continues to develop, the use of non-contact electronic monitoring may be considered. The use of photoplethysmogram technology in seclusion closed-circuit television or patients wearing wrist heart rate and movement monitors are likely to contribute to future innovation in this area (Davis et al., 2014; Kamshilin et al., 2015; Tully et al., 2015).

The relationship between physical health monitoring and psychiatric observation can be a potential source of confusion. Psychiatric observation of behaviour is often enhanced in scenarios where RT is used, with some scenarios requiring one-to-one continuous psychiatric observations. A number of levels of psychiatric observations are commonly used in psychiatric practice including: continuous arm's length, continuous line of sight and intermittent (high or low level, ranging from every 15 minutes to every 60 minutes) (NICE, 2015b). It is recommended that psychiatric observations are carried out in a sensitive manner, minimising the patient's feeling of being under surveillance (Macpherson et al., 2005). Although clearly linked, these two clinical monitoring methods (physical health and psychiatric) are not synonymous. The recommendations presented in Table 7 are for physical health monitoring (with suggested minimum psychiatric monitoring) following the use of medications pre-RT and RT and, given the dearth of evidence available, are based on the consensus of experts.

## An algorithm for the management of acute disturbance

### *Model and components*

Algorithms for the management of acute disturbance exist in the literature in the form of RT protocols and, in general,

are based on one of two models; neither is ideal. In the first type, interventions are stratified across a number of branches depending on the clinical characteristics of the acute disturbance scenario. Although these can include most clinical sub-groups, such protocols can be too unwieldy to use in an acute emergency and there is a dearth of evidence supporting stratification of patients to different interventions on the basis of their clinical presentation. Alternatively, in the second type of model, interventions are considered stepwise with a linear flow, with some reference to additional complexities related to certain clinical subgroups. However, interventions are not easily placed in a linear flow as they can be used at different points of a clinical scenario and can be used individually or often in combination.

Our algorithm includes both overarching fundamental principles and interventions (pre-RT, RT and considerations for non-response). We chose to place the interventions in a linear model with stepwise flow. This is in keeping with the general notion that there is an increased likelihood of requiring a later-stage interventional category, if earlier and generally less restrictive interventions have been tried and not had the desired outcome, the clinical state is worsening, the risks are increasing, or patient engagement is challenging.

### *Principles*

The consensus group confirmed the seven fundamental principles as outlined below.

1. **Multidisciplinary approach:** as the aetiology of acute disturbance is complex and heterogeneous, its management warrants a multidisciplinary approach including psychopharmacological, psychological, environmental and social interventions.
2. **Effective interventions:** interventions should have an evidence base confirming they increase positive outcomes and/or reduce negative outcomes (harm) of acute disturbance in the immediate to short term (from



minutes to hours). Strategies should be used to minimise the risk of adverse effects of these interventions such as seeking to prescribe the minimum effective dose and checking for increased risk of side effects.

3. **Proportionality of intervention:** an intervention has an associated imposed level of restriction on the patient and this restriction should be proportionate (i.e. not excessive) to the acute severity of the clinical risk posed by the acute disturbance. Further, the least restrictive options available should always be considered in the first instance and so RT should generally be used as a last resort only if non-pharmacological and oral pharmacological options have been exhausted.
4. **Treatment individualisation/choice:** steps should be taken, wherever possible, to ensure that interventions are selected with patient-specific factors (clinical, risk and choice related) as part of the decision-making process. This will include clinical consideration of previous response to specific medication as well as adverse responses and allergies.
5. **Treatment optimisation of underlying disorder:** interventions should be set in a context of the overarching goal of optimising the treatment of the underlying disorder as this may be partially or wholly causing the acute disturbance.
6. **Continuous monitoring/review of: (i) mental/physical health; (ii) risk to self/others; (iii) treatment effectiveness/harm; (iv) patient engagement level.** The clinical scenario and associated risks to self/others change with time. Thus, selection of interventions to reduce risk in the immediate or short term needs to reflect this so that the right intervention is used for the right scenario at the right time. Physical health is also important as both acute disturbance and the interventions are associated with physical health consequences. Further, it should be noted that when prescribing in combination some side effects are additive. As a patient-centred approach is at risk of being compromised, the assessment of the patient's level of engagement in seeking positive solutions to reduce harm and improve clinical outcomes should be kept under review.
7. **Consideration of modifiers:** certain clinical sub-populations merit specific consideration as they may require a modified approach to pre-RT and RT. These include: pregnancy, drugs and alcohol, medically frailty or physically compromised (e.g. dehydrated), psychotropic naivety, patients already prescribed regular psychotropics, learning disability and (extremes of) age.

We also note the importance of an immediate debrief and a post-incident review to consider the learning points. This should also include a review of regular medication with the aim of reducing further episodes requiring RT.

### *Recommendations for interventions*

The efficacy and key safety concerns of the putative interventions in the management of acute disturbance are summarised here, together with the categories of evidence (I–IV) and strength of recommendation (A–D, S), see also Table 1 and Figure 1.

*Pre-RT: De-escalation.* The following de-escalation components are effective: continual risk assessment, management of environment, passive intervention and watchful waiting, reassurance, respect and avoidance of shame, appropriate use of humour, identification of patient needs, distraction, reframing events for patient, non-confrontational limit setting (III; C).

The following de-escalation components may be effective: self-control techniques, avoidance of provocation, respect patient space, empathy, negotiation (IV; D).

*Pre-RT: Oral, oral-inhaled and buccal.* 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 and 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).

Pre-RT pharmacological strategies should be considered before RT (S).

*RT: IM monotherapy.* IM lorazepam is effective (Ib; A).

Parenteral benzodiazepines have safety concerns due to the risk of respiratory depression. Thus, wherever they are used, flumazenil must be immediately available (S).

IM promethazine may be effective (extrapolated Ia; D)

IM aripiprazole is effective (Ia; A).

IM droperidol is effective and a baseline ECG is advised before use due to the risk of QTc prolongation (Ib; A).

IM olanzapine is effective, but it should only be administered by itself and not concurrently with IM benzodiazepines due to risk of hypotension; thus, there should be an interval of at least 1 hour between the two (Ia; A).

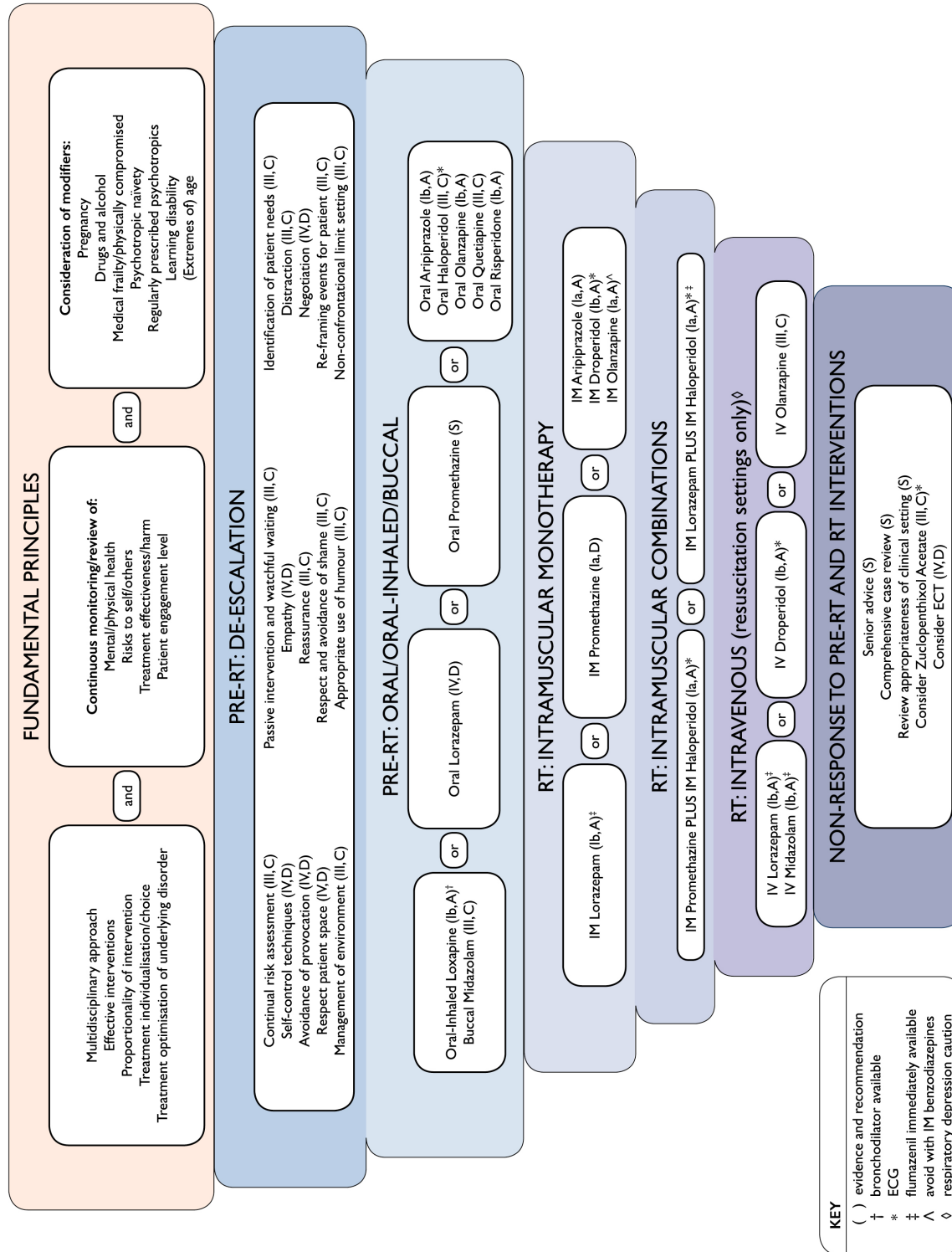


Fig. 1. An algorithm for the management of acute disturbance.

IM clonazepam is not recommended due to a relative lack of supporting evidence for use in RT (S).

IM diazepam is not recommended due to lack of evidence for use in RT (S).

IM midazolam is not recommended due to the risk of respiratory depression (Ia; A).

IM haloperidol is not recommended as monotherapy even though it has evidence of effectiveness, and a baseline ECG is advised, as measures need to be in place to offset its adverse effects and especially for the risk of acute dystonia (Ia; A).

IM levomepromazine is not recommended, even though it has some evidence of effectiveness, as there is potential evidence for a risk of cardiovascular adverse effects, especially hypotension (III; C).

RT IM monotherapy should be considered before RT IM combinations (S).

**RT: IM combinations.** IM promethazine plus IM haloperidol is effective and a baseline ECG is advised before haloperidol use due to the risk of QTc prolongation (Ia; A).

IM lorazepam plus IM haloperidol is effective and a baseline ECG is advised before haloperidol use due to the risk of QTc prolongation (Ia; A).

Parenteral benzodiazepines have safety concerns due to the risk of respiratory depression. Thus, wherever they are used, flumazenil must be immediately available (S).

IM lorazepam plus IM promethazine is not recommended due to lack of evidence for efficacy for this combination (S).

**RT: IV monotherapy (resuscitation settings only).** Due to the potential risk of respiratory depression and cardiac adverse effects, RT IV options must only be used in settings where resuscitation equipment and trained clinicians are available to manage medical emergencies (S).

Both IV lorazepam and IV midazolam are effective (Ib; A).

As flumazenil can reverse respiratory depression caused by an IV benzodiazepine, its immediate availability must be confirmed before an IV benzodiazepine is administered (S).

IV droperidol is effective and a baseline ECG is advised before use due to the risk of QTc prolongation (Ib; A).

IV olanzapine has evidence of effectiveness but caution is advised due to the risk of respiratory depression and the lack of a reversing agent (III; C).

IV diazepam is not recommended due to lack of evidence for use in RT (S).

IV haloperidol is not recommended due to a lack of evidence for its use in RT (S).

IV dexmedetomidine has evidence of effectiveness but is not recommended as it is not safe for use in settings other than possibly in medical intensive care units (Ia; A).

**Non-response to pre-RT and RT interventions.** Seeking senior advice, conducting a comprehensive case review and a reviewing the appropriateness of the clinical setting should all be considered (S).

Zuclopenthixol acetate is not recommended for use as RT as the evidence does not support it, particularly as its onset of action takes several hours. However, after other strategies have failed to achieve a required response, its use may be considered. A baseline ECG is advised before use due to the risk of QTc prolongation (III; C).

ECT may also be considered when other strategies have failed to achieve a required response, and particularly if the underlying disorder has an evidence base for the use of ECT (e.g. mania) or if there is a history of good response for the individual patient (IV; D).

IM ketamine is effective but it is not recommended due to risk of respiratory depression (III; C).

Barbiturates and valproate are not recommended due to lack of evidence for use in RT (S).

**Physical monitoring.** All patients who have received pre-RT medication should be monitored at a minimum of Low Level (S) (see Table 7).

All patients who have received IM RT should be monitored at a minimum of Medium Level (IV; D).

All patients who have received IM RT and are oversedated, asleep or significantly physically unwell, should be monitored at a minimum of High Level (S).

All patients who have received IV RT and/or are unconscious or severely physically unwell, should be monitored at Critical Level (S).

For those patients for whom direct contact physical monitoring is not safe or feasible, non-contact physical monitoring (comprising respiratory rate, level of consciousness, pallor, signs of pyrexia, evidence of dystonia/akathisia and signs of dehydration) should be conducted until direct contact physical monitoring can be established (S).

Due to the potential risk of respiratory depression and cardiac adverse effects, staff should be trained in immediate life support and resuscitation equipment use, and trained clinicians should be available to manage medical emergencies (IV; D).

## Discussion

### Overview

The management of acute disturbance in the context of an underlying mental or physical disorder presents some of the most challenging clinical scenarios in acute healthcare. The evidence base for interventions in this field remains problematic with some interventions lacking an evidence base or being only supported by evidence of lower quality

and thus consensus methods were also required. This guideline specifically focussed on the use of de-escalation methods, and non-parenteral medication used as pre-RT interventions as well as parenteral medications used in RT. We consolidated our recommendations within a clinical algorithm that included seven overarching fundamental principles that promote high-quality patient care. De-escalation was described as comprising numerous active components, each of which were considered individually with regard to the supporting evidence base. To our knowledge this guideline is the first to represent de-escalation in this way.

Historically, non-parenteral medications were included in RT, but more recently these have been relatively excluded from larger reviews and guidelines such as NG10 (NICE, 2015b). In our guideline, we have reviewed oral, oral-inhaled and buccal options and made recommendations accordingly. Parenteral medication used in RT was described across three levels: IM monotherapy, IM combinations and IV medications. Some RT medications were not recommended due to safety considerations, whereas others were recommended with specific safety advice. For IM monotherapy, IM haloperidol alone was not recommended due to risk of adverse effects including dystonia, whereas IM droperidol was recommended if the risk of QTc prolongation is taken into account by performing baseline ECG. Further, we focussed our review of the evidence for IV monotherapy in resuscitation-resourced settings such as emergency departments, acute medical and acute surgical inpatient wards in the general medical hospital.

It is important to note that several medications recommended for use in pre-RT (e.g. oral promethazine) or RT (e.g. IV droperidol) would be outside the terms of their licence (off-label) if used for the management of acute disturbance; this may be especially true for pregnant women. Thus, prescribers are advised to consult more authoritative guidance on the use of licensed medication in unlicensed situations (GMC, 2013; MHRA, 2009; Royal College of Psychiatrists, 2007, 2017).

This guideline also makes specific recommendations for monitoring of physical healthcare and psychiatric observations following pre-RT and RT medication and these include the use of non-contact physical observations where direct contact is not possible.

For scenarios where pre-RT and RT interventions have not been effective in managing acute disturbance, it is likely that the clinical picture progresses towards non-acute or prolonged disturbance. In these circumstances, we recommend seeking senior multidisciplinary advice, conducting a comprehensive case review, and reviewing the appropriateness of the clinical setting for the patient and their treatment. Zuclopenthixol acetate or ECT may also be considered, if clinically appropriate.

### *Key uncertainties and research recommendations*

One of our principles for the management of acute disturbance highlights the importance of patient-specific factors as RT medication choices should not be uniform regardless of diagnosis or clinical presentation. However, how best to individualise clinical decision making largely lacks an evidence base. Patient sub-populations should be considered, including but not limited to those who have misused substances such as NPS and pregnant women. The scope of these guidelines specifically excluded the management of acute disturbance relating to children and young people, those with learning disability or traumatic brain injury, or older adults with or without dementia. Over time, it is hoped that the evidence base for RT in these patient populations will be enhanced, allowing us to include their consideration in due course. As patient choice remains a key focus for clinical care in the UK, we also advocate further research on the perspective of patients.

We did not conduct a critical evaluation of the numerous clinical rating scales, including those used as outcome measures. We note that most focus on moderate to severe symptoms such as hostility, uncooperativeness and poor impulse control, thereby ignoring that acute disturbance is a continuum that starts with less severe symptoms such as nervousness, which progress to agitation and may or may not manifest as aggression or violent behaviour. Further consideration is warranted to identify which are the most appropriate scales to use to measure degree or frequency of acute disturbance and the outcomes of management approaches and to consider at what time points these should be evaluated. Similarly, monitoring protocols and methods, including use of technology for non-contact physical monitoring, require enhanced empirical examination.

For de-escalation, the distinct paucity of high-quality research evidence needs to be addressed to confirm the effectiveness of de-escalation as an intervention, together with exploration of the potential reasons as to why de-escalation sometimes fails. Given that failure to successfully de-escalate a situation increases the likelihood of progression to restrictive interventions and markedly increased risk for the patient and staff; any refinement of the process, active components and skills of de-escalation is important. Further, NG10 identifies the following research question as a priority: 'Which medication is effective in promoting de-escalation in people who are identified as likely to demonstrate significant violence?' (NICE, 2015b). Not only does this place due emphasis on the importance of identifying patients at risk of becoming acutely disturbed, but also notes the potential role of pre-RT medication and whether this may strengthen the use of verbal/psychotherapeutic de-escalation strategies. The interplay of oral, oral-inhaled and buccal



pharmacological interventions with de-escalation is yet to be clarified. Moreover, the difference between non-parenteral regularly prescribed or PRN medication in the management of acute disturbance warrants further investigation. Oral promethazine is commonly used as PRN medication and yet the maximum daily dose also remains subject to debate.

In our review of the evidence for RT we identified a key need for a head-to-head trial to ascertain whether there is a difference in efficacy between the combinations IM haloperidol plus IM promethazine versus IM haloperidol plus IM lorazepam. Additionally, IM promethazine may be combined with IM lorazepam and sometimes with IM aripiprazole and yet there is minimal evidence to evaluate the efficacy or harm of these combinations over their respective sole drugs alone. Also, further research on the range of IV medications is required for RT in non-psychiatric medical or surgical settings with a particular focus for medical intensive care settings and the drugs that are more familiar to clinicians working there. We also note that RCTs of RT, including the TREC studies, and naturalistic data (POMH-UK, 2017) show that a significant minority of patients do not respond to an initial attempt at RT. Thus, we ask what measures are taken by clinicians to resolve the acute disturbance for those patients? In turn, this can shape further empirical questions to be addressed by future clinical trials.

Although we found some putative interventions should not be considered as options for RT, others such as ECT treat the underlying disorder and thereby predominantly appear to have an indirect role in the management of acute disturbance. Thus, we highlight the need for further empirical research as to whether its use leads to a reduction in the risk of subsequent episodes of acute disturbance requiring RT.

### Conclusions

The management of acute disturbance is a complex process. We have presented the recommended interventions within a structured algorithm for the clinician to consider the various options according to their route of administration and category of evidence. Fundamental overarching principles are included and highlight the importance of treating the underlying disorder. Due emphasis has been placed on the phase pre-RT that includes the use of non-parenteral medication. The interplay of both pharmacological and non-pharmacological interventions, including de-escalation, is important and yet also warrants further empirical investigation. Moreover, it is noted that some medications have been somewhat disregarded for a number of years and now ought to be re-established in light of a new evidence base to support their use.

We conclude that the variety of options available for the

management of acute disturbance goes beyond the standard choices of lorazepam, haloperidol and promethazine. Ultimately, we advocate that the clinician can determine the optimal evidence-based interventions centred within a multi-faceted and multidisciplinary approach, which also includes an individualised patient perspective.

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### Declaration of conflicting interest

Declarations of potential conflicts of interest with respect to the research, authorship and/or publication of this article for all authors are available here: <https://www.bap.org.uk/RTdeclarations>

There has been no involvement of pharmaceutical companies at any stage of the development of these guidelines, from conception to publication.

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