Pharmacological Approaches for Managing Inpatient Aggression

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1 Introduction

Agitation and aggression in psychiatry have a multitude of potential causes. Some underlying causes may be internal to the patient, such as having a comorbid medical illness or substance use, and some causes may be external, such as being in a noisy, crowded or confusing environment or having a difficult interpersonal interaction with others. Prevention of aggression is paramount and cannot be overemphasised. However, when prevention fails, ideal treatment should involve and include patients as partners as early in the process as possible, for ethical reasons as outlined in other chapters, as well as to minimise the risk of harm to patients and others.

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Several treatment approaches regarding inpatient aggressive behaviour exist, including psychopharmacological and behavioural methods (Bak et al., 2019). Specific brain circuits have been proposed to underlie aggressive behaviour, particularly the amygdala, limbic prefrontal regions and the connection between the two (Aleyasin et al., 2018). Additionally, multiple neurotransmitters, including serotonin and dopamine, have been hypothesised to be involved, based on animal and human models of aggression (Yanowitch & Coccaro, 2011). Given the magnitude of the problem and the limitations of our knowledge, a broad range of medications has been investigated for anti-aggressive properties (Bak et al., 2019). However, despite the high prevalence of the use of medications to address psychiatric inpatient aggression, evidence for the efficacy of the pharmacological management of aggressive behaviour is currently lacking (Gaynes et al., 2017).

In this chapter, we begin with a brief overview of medication use in psychiatric emergencies. We then concisely describe the neurobiology, neurophysiology and anatomy of aggression. Subsequently, we summarise recent systematic reviews, meta-analyses and national guidelines addressing the pharmacotherapy of aggression in general adult psychiatry. We conclude the chapter with a description of the experience of rapid tranquillisation written by a person with lived experience and make recommendations for the conduct of future research.

In this chapter, the person with lived experience was not involved in the writing of the rest of the chapter. However, their balanced description of their experiences, at the end of the chapter, reflects many of the key points raised. They state that it is not unreasonable to become agitated when one has lost some rights and freedoms, and that with a well-trained and led staff, giving the person space can result in them calming themselves without need for medication. Further they state that prn meds and rapid tranquillisation should be used only in the most extreme situations, once all other options have been tried, and that the use of such methods should be well-thought-out and reasoned. We are grateful for their contribution.

2 Overview of Medication Use in Psychiatric Emergencies

Using pharmacologic agents to reduce acute agitation in patients living with psychiatric illnesses remains controversial because they are often given without a patient's consent. When parenteral, rather than oral, medication is used (Hirsch & Steinert, 2019; Kim et al., 2021), this practice is sometimes called 'rapid tranquillisation' (RT) (Zareifopoulos & Panayiotakopoulos, 2019). RT should be reserved only for patients in acute distress who are agitated, combative or otherwise at risk for violent behaviour *and* unable to engage in or benefit from de-escalation attempts. The indication for immediate intervention such as RT is that there is a high potential risk to the patient and others around them. Clinicians should maintain awareness that RT may be harmful as it could lead to undesirable medical or psychological side effects and legal conflicts and could undermine the clinician–patient relationship. Deciding whether or not to use RT must also take into account the patient's underlying psychiatric illness(es) and physical health status, as well as the need for timely resolution of the situation, due to the emergent risk of harm to the patient or others. As

such, all clinicians should be familiar with available RT options, the side effects associated with each, the duration of action, routes of administration and the empirical evidence regarding their use in such a setting (Zareifopoulos & Panayiotakopoulos, 2019). Furthermore, the legal and ethical conditions under which RT may be implemented differ from country to country, and because there is limited evidence regarding the efficacy of specific agents, is largely dependent on clinical judgement and what medications are available (Hirsch & Steinert, 2019).

3 Neurobiology of Aggression

The literature proposes that violence is a heterogeneous behavioural response to the interpretation of environmental stimuli and threats, a response that is also influenced by the social, neurobiological and environmental context of the individual (Manchia et al., 2020). Current knowledge suggests that reactive and proactive violence depends on the activation of different brain circuits and neurotransmitter systems (Romero-Martínez et al., 2022). Among them, the more solid evidence points towards the serotonin (5-HT) system in terms of changes in 5-HT levels and 5-HT receptor function, but also genetic and epigenetic modifications at the level of the enzymes involved in the synthesis, degradation and/or reuptake of 5-HT (Pavlov et al., 2012; Romero-Martínez et al., 2022). However, no definitive predictive biomarkers of violent behaviour have yet been identified (Manchia et al., 2020; Pinna & Manchia, 2017). For this reason, future studies in large and controlled clinical and community populations examining genetic and epigenetic markers as well as behavioural-cognitive, brain imaging and metabolomics signatures of violence are needed (Caruso et al., 2021).

3.1 Neuroanatomy

Studies on the neuroanatomical substrates of aggression have proposed possible alterations in brain areas also involved with the formation of psychotic symptoms and affective regulation, including frontotemporal circuitry, the amygdala-orbitofrontal system, prefrontal cortex and hippocampus (Fjellvang et al., 2018; Manchia et al., 2017; Pompili et al., 2017; Widmayer et al., 2018, 2019). The corticolimbic network has been suggested to play an important role in aggression and violence, as the amygdala plays a key role in perceiving and interpreting threat stimuli in the surrounding environment (Manchia et al., 2020). This network represents the connection between brain areas in the cortical region, such as the anterior cingulate cortex (ACC), the prefrontal cortex (PFC) and the insula and amygdala.

3.2 Neurotransmitters

Several decades of preclinical and clinical research have demonstrated a central role for different neurotransmitters and neuromodulators in the neurobiology of violence. Biogenic amines including serotonin (5-HT), norepinephrine (NE),

dopamine (DA), glutamate and GABA, as well as neuropeptides such as substance P, vasopressin and oxytocin, all appear to play a key modulating function in violent behaviour (Manchia et al., 2020). Multiple lines of evidence have shown dysfunction in the serotonin (5-HT) system in aggressive and in mentally ill subjects, with reduced 5-HT activity associated with depression as well as with impulsive aggression (Comai et al., 2016; Gowin et al., 2013). Central nervous 5-HT has been studied using challenge techniques; such techniques have been demonstrated to alter amygdala activity in response to threatening stimuli, or stimuli that may elicit violence. Responses from the amygdala then activate or dampen activity in the surrounding cortices; however, such responses differ, depending on the type of violence being exhibited (Manchia et al., 2020).

The contributing role of steroid hormones is another focus of recent research. In a multiple regression model including abuse/neglect history, psychopathy and impulsivity, baseline cortisol explained 58% of the variance in trait aggression (a chronic, long-standing personality characteristic) and 26% of the variance in state aggression (temporary, short-lasting outbursts of anger) (Gowin et al., 2013). These findings support the hypothesis that adverse childhood experiences may predict a reduced hypothalamus-pituitary-adrenal (HPA)-axis reactivity, leading to the possibility that a history of child maltreatment, psychopathy and an impaired HPA-axis reactivity might act synergistically in the production of aggressive behaviour (Haller et al., 2014; Toth et al., 2011). Recently, pathological appetitive aggression, in which positive feelings are associated with perpetrating violent behaviour, has been hypothesised to result from excessive activation of evolutionarily conserved reward circuits, also mediating the rewarding effects of addictive drugs (Golden & Shaham, 2018). The authors suggest that inappropriate appetitive aggression shares core features with addiction: aggression is often sought despite adverse consequences, and relapse rates among aggressive offenders are as high as relapse rates in drug addiction (Golden & Shaham, 2018). Pathological appetitive aggression is distinguished from defensive aggression, which is a fear response to a perceived threatening situation, and there are no positive feelings associated with the aggressive act.

3.3 Genetics

Several genes have been investigated to explore a possible correlation with aggressive behaviour. The most intensively studied is the catechol-O-methyltransferase (COMT) gene on chromosome 22. COMT is involved in the metabolism of dopamine, one of the neurotransmitters hypothesised to be involved in the production of the symptoms of schizophrenia. A meta-analysis involving 2370 individuals showed that male patients with schizophrenia who carried the low-activity methionine allele in the COMT gene had an increase in aggression risk of approximately 50% compared with homozygous valine patients (Singh et al., 2012). A more recent Swedish cohort study was concordant with the hypothesis that COMT genotypes modify the sensitivity to the environment that confers either risk (methionine allele) or protection (valine allele) for aggressive behaviour (Tuvblad et al., 2016).

4 Brief Review of Most Common Medications Used

There are various reasons why the evidence base for the most effective pharmacologic management of acute aggression is sparse. First, because of the potential dangers associated with violence, gold-standard randomised-controlled trials (RCTs), especially RCTs with large numbers of participants, evaluating new treatments, are few. Second, there is no consensus regarding outcome measures when treating violence, leading to considerable heterogeneity in existing studies. Thus, while neurotransmitters are the putative targets of pharmacologic treatment of aggression, current practice is still somewhat a matter of trial and error, with broad guidelines for classes of medications to use. In this section, we summarise the most commonly used types of medications, the ways that they are used, and describe systematic reviews and published guidelines for their use. Finally, based on these reviews and guidelines, we offer general recommendations for the use of psychopharmacologic agents in addressing acute aggression.

4.1 Benzodiazepines

Benzodiazepines are a class of medications used primarily as anxiolytics and soporifics; they are also used acutely to treat seizures. They facilitate the binding of GABA, an inhibitory neurotransmitter, throughout the central nervous system, essentially 'slowing down' activity in the brain. At lower doses, most benzodiazepines will cause some sedation, and at higher doses, can induce sleep. The differences between the various benzodiazepines are primarily in metabolism; longer-acting medications such as diazepam have half-lives between 40 and 250 h, intermediate-acting medications such as lorazepam have half-lives between 12 and 40 h, and shorter-acting medications such as midazolam have half-lives between 1 and 12 h (Griffin et al., 2013). Lorazepam is often used for rapid tranquillisation in part because of its safety profile; while several other benzodiazepines continue to have an effect in the body for up to days after administration, lorazepam has a relatively shorter time of effect, in particular with those who have liver disease. Lorazepam is available in injectable form (intravenous, or IV, and intramuscular, or IM), sublingual and in liquid or pill form.

4.2 Antipsychotic Medications

First- and second-generation neuroleptic medications, also called antipsychotic medications, belong to classes of medications that block dopamine receptors in the brain (first-generation) or combinations of dopamine and serotonin (second-generation). They are used to treat symptoms of psychosis, often in the context of schizophrenia, bipolar disorder and depression. They can be used acutely to treat mania and adjunctively in the treatment of bipolar disorder and major depression. The major difference between first- and second-generation antipsychotic medications is in their likelihood

of causing certain side effects. First-generation medications are more likely to lead to movement disorders such as tardive dyskinesia and extrapyramidal symptoms. Second-generation medications, with a couple of exceptions, are more likely to lead to metabolic dysfunction—hyperlipidemia, weight gain and type II diabetes mellitus. In addition to pill and liquid forms, many antipsychotic medications are available for acute and long-acting intramuscular (IM) administration. While antipsychotic medications such as haloperidol are commonly used to manage acute agitation and aggression in psychiatric settings, the mechanism of action is unknown. Hypothetical mechanisms include sedation leading to the reduction of agitation, dopamine blockade leading to the reduction of underlying psychosis, and at higher doses, first-generation antipsychotic medications are similar in structure to GABA, thereby slowing brain activity (Wilson et al., 2012).

4.3 Anticholinergic and Antihistaminergic Medications

Anticholinergic and antihistaminergic medications such as benztropine and diphenhydramine are frequently used in the context of the management of aggression as adjunctive medication to antipsychotic medications in order to prevent or manage extrapyramidal symptoms, such as dystonia, akathisia and parkinsonism. They are sometimes used on their own to manage aggression, although the mechanism of action is primarily through sedation and reduction of involuntary muscle movement due to acetylcholine blockade. These medications can have side effects of sedation, dry mouth and blurred vision, among others. Many anticholinergic and antihistaminic medications are available in pill, liquid and IM form.

4.4 Additional Medications

Droperidol is a dopamine antagonist related to haloperidol that is used to prevent and treat postoperative nausea and vomiting. It has been used primarily in the ED as a sedative or tranquilliser via the IM or IV route in patients with acute agitation, as it has a more rapid onset and shorter duration of action than haloperidol. In 2001, the FDA issued a black box warning about the risk of QT prolongation, and the drug fell out of common use. However, two large retrospective studies showed no increase in mortality or morbidity for droperidol when used at doses of 5–10 mg (Perkins et al., 2015).

4.5 Summary of Systematic Reviews

In order to update their 2015 guidelines for the treatment of acute agitation, the National Institute of Health and Care Excellence (NICE) identified nine systematic reviews of medication comparisons (NICE, 2019). Of these, six were Cochrane Reviews, all of which included people with agitation in the context of psychosis. The only study citing high-quality evidence was by Khokhar and Rathbone (2016), in

which they concluded that IM droperidol was more effective than placebo in achieving tranquillisation after 30 min, with comparable side effects to placebo. The remaining studies reported mostly low and low to medium quality evidence, largely due to problems with bias. The remaining studies are summarised in the following paragraph.

Haloperidol plus promethazine was reported as more effective at causing sedation at 30 min as compared to lorazepam or haloperidol alone, with no significant difference between the effects of haloperidol plus promethazine, ziprasidone or olanzapine (Huf et al., 2016). No difference was found regarding efficacy or adverse effects of IM risperidone versus IM haloperidol and IM olanzapine after 24 h; there was no difference between aripiprazole and haloperidol but aripiprazole required more injections to achieve sedation; and aripiprazole was more effective than placebo and less effective than olanzapine at 2 h post-IM (Ostinelli et al. 2017, 2018b, b). Another review concluded there was no significant difference between benzodiazepine, placebo or haloperidol IM in the short term, and in the medium term, benzodiazepine IM was more effective than placebo. Also, while there was no significant difference in the effectiveness of a benzodiazepine plus haloperidol versus either benzodiazepine or haloperidol alone in the short term, sedation was more likely in the group that received benzodiazepine plus haloperidol versus haloperidol alone (Zaman et al., 2017). One review found a difference between treatments: haloperidol plus promethazine, olanzapine and droperidol were the safest and most effective at reducing agitation within 2 h, although there were more adverse effects with haloperidol and haloperidol plus lorazepam (Bak et al., 2019). Neither of the two remaining papers showed any difference in efficacy or adverse effects of haloperidol, olanzapine, aripiprazole, loxapine and lorazepam IM (Dundar et al., 2016; Kousgaard et al., 2017).

4.6 Guidelines for the Pharmacotherapy of Aggression

In our efforts to compile the most up-to-date guidelines for the pharmacotherapy of aggression, we searched recent systematic reviews and meta-analyses, and hand-searched references from each to find listed guidelines (Bak et al., 2019; Cowman et al., 2017; Muir-Cochrane et al. 2020a, b; NICE, 2015, 2019; Roppolo et al., 2020). We selected guidelines for the pharmacologic management of aggression based on available research evidence when possible, and on consensus when research was limited. These guidelines were authored by experts from various regions, including North America, Europe, the UK and Latin America.

The 2005 *Expert Consensus Guidelines: Treatment of Behavioral Emergencies,* aimed at clinicians who work with clients who become aggressive or agitated, were derived from survey responses from 48 leading American experts on psychiatric emergency medicine (Allen et al., 2005). According to the guidelines, an ideal medication to treat agitation would be 'non-invasive and easy to administer, have a rapid onset, calm without sedating, address underlying symptoms and have a favourable tolerability and safety profile' (Allen et al., 2005; Martínez-Raga et al., 2018). In general, guidelines recommend initially assessing for any underlying medical cause of agitation and aggression and treating if possible (Garriga et al., 2016; Roppolo

et al., 2020). Benzodiazepines are recommended for patients with undifferentiated agitation and aggression due to alcohol withdrawal, while antipsychotic medication is recommended for clients exhibiting psychotic symptoms and low-dose antipsychotics for delirious agitated patients (Roppolo et al., 2020).

The first International Experts' Meeting on Agitation in October 2016 in Madrid was attended by 20 experts from Europe and Latin America who had clinical experience managing acute agitation (Martínez-Raga et al., 2018). This group identified the lack of universal protocols or guidelines, lack of education and training of providers and limited available clinical data as considerable barriers to treating agitation properly. A poll of attendees found that antipsychotic medications were used more than 50% of the time, with benzodiazepines second most common. An increasing trend in the use of inhaled antipsychotic medications was noted, although their use was not yet widespread (Martínez-Raga et al., 2018). Most importantly, this group emphasised focusing on client-centred care and the service user experience, indicating that medication should be non-traumatic/non-coercive and that whenever possible, client preference should guide choice (Martínez-Raga et al., 2018). This group of international experts agreed that the ideal time to intervene with medications would be as early as possible in the cycle of increasing agitation, between the low-moderate to mid-moderate level of severity; however, they noted that client and caregiver preference was for pharmacologic intervention during mild agitation (Martínez-Raga et al., 2018). They concluded that the benefits of early intervention outweigh the risks, and strongly recommended this as a course of action (Martínez-Raga et al., 2018).

The National Institute for Health and Care Excellence (NICE) in the UK has written guidelines for short-term management of acute agitation in psychiatric settings that were developed by a multidisciplinary team of healthcare professionals, clients with a personal experience of aggressive behaviour, their caregivers and guideline methodologists (NICE, 2015). NICE performed a systematic review of rapid tranquillisation based on data from a series of Cochrane reviews (NICE, 2015) with permission from the publisher, and with assistance from the Cochrane Schizophrenia Group, into one review which was analysed according to the strategy in the review protocol. Their recommendations are to use lorazepam IM alone or with IM haloperidol plus IM promethazine for RT in adults (NICE, 2015). They state that the choice of medication should be driven by the service user's preferences, comorbid physical health issues, possible intoxication, previous response to medications, the potential for interactions with other medications and the total daily dose of medications that the person has taken (NICE, 2015).

5 Recommended Pharmacologic Strategies to Address Acute Aggression

5.1 Pro Re Nata (PRN) Medication

Oral and parenteral medications can be used as preventatives as well as for acute treatment of agitation and aggression. Often referred to as PRN (for the Latin term pro re nata, meaning 'as the circumstance arises'), such medications and their route of administration should be agreed upon in advance in collaboration with the patient

(McDougall et al., 2022). However, in practice, such medications are often prescribed routinely without consulting patients, as prophylaxis to prevent aggressive and violent incidents in hospitals (Mardani et al., 2022). Unfortunately, these can be used in a coercive manner—e.g. 'either you take this med or go into seclusion'—or to 'medicate' understandable behaviours that could be addressed through other means (McDougall et al., 2022). While the use of PRN medication is widespread in psychiatry, there is little evidence in the literature regarding its effectiveness (McDougall et al., 2022; Patel et al., 2019); this may be because performing randomised-controlled trials with this population for acute aggression is difficult.

Given the prevalence of PRN use, we present a summary of the NICE guidelines that have been written regarding prescribing PRN medication as part of a strategy to de-escalate or prevent situations that may lead to violence and aggression. NICE recommends that PRN medication should not be prescribed routinely or automatically on admission and should be individualised to the specific needs of the client after discussion with the client if possible. When PRN medication is prescribed, it should be clearly written in the care plan and the prescription itself under what circumstances it is to be offered, with specific intervals between doses, identifying the maximum daily dose. The NICE guidelines state that the maximum daily dose should not exceed that specified by the British National Formulary when combined with the person's standard dose or their dose for rapid tranquillisation and should be exceeded only if this is planned to achieve an agreed therapeutic goal, documented and carried out under the direction of a senior prescribing individual. Further, NICE recommends that the clinical team should review PRN medication at least once a week including a written rationale for continuation. If PRN medication has not been used since the last review, NICE recommends consideration of stopping (NICE, 2015).

5.2 Recommended Strategies for Pharmacotherapy in Acute Agitation

Rapid tranquillisation (RT) is defined as the administration of sedative medication by injection (Hirsch & Steinert, 2019; Zareifopoulos & Panayiotakopoulos, 2019). Most reviews describe a lack of sufficient evidence to support any particular approaches to treat aggression via medications, explaining that most studies remain descriptive or compare a small number of agents (de Almeida et al., 2017; de Souza et al., 2022; Hirsch et al., 2021). They also noted that reported outcomes were not consistent across studies, using a variety of measures and criteria. While there were differences in specific algorithms and recommendations between guidelines, there were some common principles. These included paying attention to the service user experience and working in partnership with service users and their carers, adopting approaches to care that respect service users' independence, choice and human rights, and increasing social inclusion by decreasing exclusionary practices, such as the use of seclusion. In the best of situations, a service user would be able to create an individualised pharmacological strategy to reduce the risk of, or address directly, violence and aggression. This would be in collaboration with a multidisciplinary team that develops the specific plan, with doses, timing, target symptoms and regular reviews of the plan, taking into account the service user's preferences and values (NICE, 2015). As there is no

evidence showing clear superiority for any specific medication or combination, individualised treatment needs to be emphasised, taking into account the service user's view, pre-existing physical health problems, previous response to medications including adverse effects, the potential for interactions with other medications and the total daily dose of medications prescribed and administered (NICE, 2015). Per NICE guidelines, IM lorazepam is recommended for service users who have not taken antipsychotic medication before because it is an effective intervention that is likely to be acceptable to most people. Prescribing an initial, single dose ensures that any subsequent treatment options can be individualised, taking account of both response and any emergent adverse effects of the initial treatment choice (NICE, 2015).

The NICE (2015) algorithm recommends first taking into account the client's preference for medication and route of administration in the context of RT. If the client has no experience with antipsychotic medication, NICE recommends the use of lorazepam. If there is a partial response to lorazepam, consider another dose; if there is no response, consider IM haloperidol plus IM promethazine. If the client has a partial response to haloperidol plus promethazine, consider another dose if needed. If there is no response to IM haloperidol plus promethazine, consider IM lorazepam if that has not already been used. If IM lorazepam has already been used, then further review with the team and expert opinion should be sought. In the case of prolonged QT interval, or no electrocardiogram results, avoid IM haloperidol plus promethazine and use IM lorazepam. NICE further recommends that after RT, side effects, vital signs and levels of hydration and consciousness should be monitored at least hourly until there are no further physical health concerns (NICE, 2015). They also recommend increasing monitoring to every 15 min if the maximum dose has been exceeded, the service user is sedated, is suspected of having taken illicit substances or alcohol, has a pre-existing health condition or has previously experienced harm resulting from any restrictive intervention.

6 Special Populations and Situations

6.1 Older Adults

The European Academy of Neurology recommends that when agitation and aggression exist when someone has a form of dementia, this should only be treated with atypical antipsychotic medications after non-pharmacologic methods have been exhausted or there is an imminent risk of severe self-harm/harm to others (Frederiksen et al., 2020). They also make a 'weak recommendation' to stop antipsychotic medications as soon as possible, citing this as good practice.

6.2 Violence in the Emergency Department

The very small number of research studies involving the management of aggression in emergency department settings has been summarised as not adequate to provide a framework for evidence-based practice in these settings (Fricke et al., 2022; Taylor & Rew, 2011). However, we found an additional review and network meta-analysis

studying the most optimal medication treatment of acute agitation in the emergency department. Their concerns were safety and time to tranquillisation, and they concluded that while ketamine and droperidol have intermediate effectiveness, high-quality evidence is lacking to support either one as safer or more effective (de Souza et al., 2022).

7 Personal Experience with Medication, Chris Munt

Many patients who are admitted to mental health units have personal experience or knowledge as to the use of PRN and rapid tranquillisation medications. The management of such interventions appears to many who have been detained or admitted on a voluntary basis to be unclear, inconsistent and used primarily to make patients docile and compliant. There is a consensus that such arrangements at best are an example of care through control; at worst it's exploiting those who lack the resources to challenge such decisions. Taking into account the natural emotions associated with being removed from society, your liberty suspended, rights curtailed, and placed into an environment that appears somewhat clinical, with non-negotiable routines and procedures, is it no wonder that sometimes these individuals will express their shock, frustration, confusion in a loud, animated and disturbing manner? It is entirely possible that with the right environment, with a skilled, experienced and well-led workforce, these natural responses might be viewed as natural given the context, and even part of a healing process, rather than internalising those feelings and emotions. I have experienced different teams on the same ward having vastly different tolerances to such behaviours, and from my observations, the teams that will not defer to PRN as the first or second response will have a similar outcome for the patient, which is a gradual reduction of behaviours of concern whether PRN is dispensed or not.

Over two decades, I experienced multiple admissions to such institutions. I experienced countless incidents of being given PRN medication. Most of the time I complied, but whenever I refused, it was made clear that to do so would result in my detention, even though I was always admitted as a voluntary patient and had the right to choose whether or not to take medication. On too many occasions, I observed this abuse of power taking place with other patients, through explicit or implicit threats. Though thankfully not routine, I was witness to incidents of physical restraint on patients followed by rapid tranquillisation. Such events are not easily erased from my memory, and the trauma experienced by the victim is an anathema in the context of therapeutic and humane treatments.

Many patients in my experience maintain that some staff take an enthusiastic part in such restrictive interventions, while some will conduct themselves professionally, with the patient front and centre of their concerns. I have observed patients taking 24 h to recover from tranquillisation with no clear memory of what happened and what led to the incident. Therefore, there is no learning for that individual other than a legacy of fear and suspicion.

I'm not anti-medication and recognise that it has its place in what should be a suite of options for both the patient and the professional. But they should be tailored to the individual and closely scrutinised and managed. We should have more concordance in prescribing medications, as a key flaw in the arguments for compliance

is that under such regimes, patients tend to stop taking their meds when unsupervised. If we engage patients in the prescribing progress and understand their fears or resistance, we might find that patients will take their medications in both supervised and non-supervised conditions.

In summary, we should better demonstrate the use of PRN and rapid tranquillisation only when other approaches have been considered and deployed. In addition, those dispensing these medications must articulate a rationale for doing so and such incidences should be properly scrutinised to establish trends and patterns associated with different staff and different teams.

8 Recommendations for Future Research

This chapter shows that the body of evidence accumulated from RCTs is lacking. Statistical power is low in many studies due to the small number of participants and the generalisability of results to daily clinical practice can be difficult, due to the limited inclusion criteria for studies. We recommend that future large-scale pragmatic trials will be conducted which include people with lived experience as research partners in the endeavour. Further, we suggest the following as particular topics to be explored:

1. Is the use of medication more effective than other methods in promoting de-escalation in people who are identified as likely to demonstrate significant violence?
2. What forms of management of violence and aggression do service users prefer and what roles do advance statements and decisions have in management and prevention?
3. What guideline and algorithm adaptations are needed in the management of aggression and violence in the context of substance use and withdrawal?
4. What guideline and algorithm adaptations are needed for specific health settings, such as in the emergency department, on a general hospital ward or in a secure psychiatric facility?
5. What are novel methods for the delivery of medications in acute agitation (for example, intranasal or epidermal administration)?
6. What are the long-term effects and side effects of RT?
7. How useful is PRN medication in preventing violence or in aiding the ability of the service user to engage in de-escalation more readily?

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