Original Paper

The pharmacological management of acute behavioural disturbance: Data from a clinical audit conducted in UK mental health services

Journal of Psychopharmacology
2019, Vol. 33(4) 472–481

DOI: 10.1177/0269881118817170
journals.sagepub.com/home/jop

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Abstract

Background: A quality improvement programme addressing prescribing practice for acutely disturbed behaviour was initiated by the Prescribing Observatory for Mental Health.

Method: This study analysed data from a baseline clinical audit conducted in inpatient mental health services in member trusts.

Results: Fifty-eight mental health services submitted data on 2172 episodes of acutely disturbed behaviour. A benzodiazepine alone was administered in 60% of the 1091 episodes where oral medication only was used and in 39% of the 1081 episodes where parenteral medication (rapid tranquillisation) was used. Haloperidol was combined with lorazepam in 22% of rapid tranquillisation episodes and with promethazine in 3%. Physical violence towards others was strongly associated with receiving rapid tranquillisation in men (odds ratio 1.74, 1.25–2.44; $p<0.001$) as was actual or attempted self-harm in women (odds ratio 1.87, 1.19–2.94; $p=0.007$). Where physical violence towards others was exhibited, a benzodiazepine and antipsychotic was more likely to be prescribed than a benzodiazepine alone (odds ratio 1.39, 1.00–1.92; $p=0.05$). The data suggested that 25% of patients were at least 'extremely or continuously active' in the hour after rapid tranquillisation was administered.

Conclusion: The current management of acutely disturbed behaviour with parenteral medication may fail to achieve a calming effect in up to a quarter of episodes. The most common rapid tranquillisation combination used was lorazepam and haloperidol, for which the randomised controlled trial evidence is very limited. Rapid tranquillisation prescribing practice was not wholly consistent with the relevant National Institute for Health and Care Excellence guideline, which recommends intramuscular lorazepam on its own or intramuscular haloperidol combined with intramuscular promethazine. Clinical factors prompting the use of rapid tranquillisation rather than oral medication may differ between the genders.

Keywords

Rapid tranquillisation, acute behavioural disturbance, aggression, antipsychotic medication, benzodiazepine

Introduction

Acutely disturbed behaviour is common in psychiatric inpatient settings and can put both patients and others at risk. Where de-escalation and other non-pharmacological strategies prove to be ineffective, psychotropic medication is often administered. It is generally accepted that the aim of such a pharmacological intervention is to produce calmness rather than specifically treat any underlying mental illness, although this treatment target is not consistently supported by relevant clinical guideline recommendations (Garriga et al., 2016; National Institute for Health and Care Excellence, 2015). However, all existing evidence-based treatment guidelines do agree that oral medication should be offered in the first instance and the parenteral route only used when a patient is unwilling to co-operate and/or there is an urgent need to reduce clinical risk (Garriga et al., 2016; Holloman and Zeller, 2012; National Institute for Health and Care Excellence, 2015).

Acute behavioural disturbance covers a spectrum from behavioural over-activation, with 'signs of overt physical or verbal activity that calms down with instructions' at one end, through to 'extremely or continuously active, not requiring restraint' and 'violent, requires restraint' (Swift et al., 2002) at the other. Non-pharmacological interventions should always be considered and may effectively calm patients whose behaviour is at any point on this spectrum, although such strategies may be presumed to be less feasible and less helpful in those who are the most behaviourally disturbed. How, and to what extent, the clinical picture of an acute behavioural disturbance, including the level of behavioural activation, influences the choice of medication regimen in routine care remains uncertain.

In clinical practice, oral medication for emergent episodes of agitation or anxiety may be requested by patients or offered by nursing staff to both manage symptoms of this nature and prevent exacerbation, although the evidence base supporting the use of such 'as required' or 'pro re nata' (PRN) medication is poor (Douglas-Hall and Whicher, 2015). The point at which PRN medication

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becomes rapid tranquillisation (RT) is poorly defined in the international literature. In the UK, the National Institute for Health and Care Excellence (2015) defines RT as the 'use of medication by the parenteral route…if oral medication is not possible or appropriate and urgent sedation with medication is needed' (page 217).

Regarding which medication to use, the National Institute for Health and Care Excellence recommends either intramuscular (IM) lorazepam alone or IM haloperidol in combination with IM promethazine, the choice being informed by a patient's clinical circumstances such as any physical health conditions, use of substances, history of response to and tolerability of medication, and their preference, which may be available as an advance statement. This recommendation is based on the four, pragmatic TREC studies that compared a combination of parenteral haloperidol and promethazine with either IM haloperidol alone (Huf et al., 2007), IM olanzapine alone (Raveendran et al., 2007), IM lorazepam alone (Alexander et al., 2004) or IM midazolam alone (Tranquilização Rápida-Ensaio Clínico [TREC] Collaborative Group, 2003). However, a recent consensus document produced by the World Federation of Societies for Biological Psychiatry (Garriga et al., 2016) recommends selecting medication based on the perceived aetiology of the behavioural disturbance, with an antipsychotic recommended where a patient has a psychotic illness or has taken illicit substances, and a benzodiazepine when substance withdrawal or anxiety are present.

The Prescribing Observatory for Mental Health (POMH-UK) coordinates audit-based quality improvement programmes (QIPs) addressing aspects of prescribing practice in mental health services. In 2016, the baseline audit was conducted for a QIP on prescribing for acute behavioural disturbance. The data collected provided the opportunity to describe the medication regimens used to manage episodes of acute behavioural disturbance in routine clinical care in a large sample of mental health services in the UK.

Aims of the study

1. To describe the medication regimens used to manage episodes of acute behavioural disturbance in routine clinical care in mental health services in the UK.
2. To explore whether particular demographic and clinical variables are associated with the medication regimen administered.

Materials and methods

In 2016/17, all 86 National Health Service (NHS) mental health trusts and other healthcare organisations providing inpatient mental health services in the UK which we could identify were invited to become members of POMH-UK and participate in POMH-UK quality improvement programmes. All 64 organisations that elected to join were invited to participate in an audit-based QIP focusing on prescribing for acutely disturbed behaviour. The clinical practice standards for the audit were derived from the NICE NG10 guideline (National Institute for Health and Care Excellence, 2015), agreed by all the co-authors and discussed and refined at UK regional workshops attended by representatives of participating mental health trusts. The standards related to the quality of care planning, avoidance of parenteral haloperidol in the absence of a recent electrocardiogram (ECG) and physical health monitoring in the period immediate following the administration of parenteral medication. The collection of data that directly assessed performance against these practice standards was a key element of baseline audit, conducted as part of this quality improvement work, but these data are not described here. This article reports on the additional contextual data collected in the audit, specifically information on the manifest symptoms and behaviours at the time of the clinical decision to administer additional medication and the particular medicines that were administered

Over a two-month period, each participating mental health service was asked to identify episodes of acutely disturbed behaviour for which additional psychotropic medication had been administered and then promptly collect the following data for each such episode: the patient's year of birth, gender, ethnicity, psychiatric diagnoses and legal status with respect to mental health legislation; type of clinical service providing care; non-pharmacological interventions used in the episode; symptoms and behaviours displayed at the time of the episode; level of behavioural disturbance (applying the descriptions of the categories in the Behavioural Activation Rating Scale (BARS) (Swift et al., 2002); regularly prescribed medication; medication administered for the episode of acutely disturbed behaviour and route of administration; and level of behavioural disturbance after medication was administered.

To avoid the data being skewed by a small number of patients who may have received additional psychotropic medication on multiple occasions over a short period of time, the pragmatic decision was taken to ask services to submit data for one episode for any given patient unless the episodes were separated by at least seven days. We therefore report information at the level of episodes of disturbed behaviour rather than individual patients.

Data submission and analyses

Anonymised data were submitted on-line between September–November 2016 using Formic software (Formic Software, 2016) and analysed using SPSS (IBM, 2017). To allow the accuracy of data entry to be checked, each participating mental health service was sent a copy of their submitted dataset along with any data-cleaning questions.

The demographic and clinical characteristics of the patients who had received medication to manage an episode of acutely disturbed behaviour were analysed using descriptive statistics only.

With respect to regularly prescribed antipsychotic medication, for each episode, the daily dosage that the patient was prescribed was converted into a percentage of the maximum licensed dose (and, if more than one antipsychotic was prescribed, the percentages were added together), to determine whether this represented a standard or high dose (Royal College of Psychiatrists, 2014). Where an antipsychotic was administered to manage an episode of acute behavioural disturbance, the percentage of its maximum daily dose was added to that of any regularly prescribed antipsychotic medication to determine whether this additional antipsychotic medication resulted in the patient's total antipsychotic dosage reaching the high-dose threshold on that day.

Logistic regression analyses were used to explore whether any of the demographic and clinical variables collected were associated with the choice of medication route (oral or parenteral). These analyses were performed separately for men and

women. Route of administration (oral or parenteral) was the dependent variable while the independent variables were ethnicity, age (in 10-year bands), psychiatric diagnoses (using the International Classification of Diseases [ICD10] categories), legal status with respect to mental health legislation, the nature of the clinical service providing care, the nature of the symptoms and behaviours present at the time of the episode, and the level of behavioural disturbance (using BARS descriptors). A further binary logistic regression analysis was performed with the choice of the medication regimen (an IM benzodiazepine alone or an IM benzodiazepine combined with an IM antipsychotic) as the dependent variable with the independent variables being the same as in the previous analyses, but with the addition of gender. This analysis was repeated, with the choice between an IM antipsychotic alone and an IM antipsychotic combined with an IM benzodiazepine as the dependent variable. For each of the four binary logistic regression analyses, a set of univariable analyses was performed initially to examine the associations between the independent variables and each of the dichotomous dependent variables. These associations were then examined in multivariable analyses using a backwards selection procedure to retain only the statistically significant variables.

Results

Fifty-eight specialist mental health services participated in the baseline audit, submitting data for 2172 episodes of acutely disturbed behaviour. For 1091 episodes, oral medication only was administered to treat the episode while for the remaining 1081 episodes parenteral medication was used. The demographic and clinical characteristics of the patients who received oral and parenteral medication for an episode of acutely disturbed behaviour are shown in Table 1.

Non-pharmacological interventions

One or more non-pharmacological interventions were used in 2062 (95%) episodes; these were verbal de-escalation and/or distraction and/or the removal of precipitating factors (1842 episodes; 89%), an increased level of observation (934; 45%), control and restraint (880; 43%), use of a recognised ‘time out’ area (348; 17%), seclusion in a designated seclusion room (295; 14%), supervised confinement (227; 11%) and transfer to a more secure setting (97; 5%).

Why was medication administered?

For 2000 (92%) cases, sufficient information was available regarding the level of behavioural disturbance displayed by the patient prior to the administration of medication to allow a baseline BARS score to be determined. Of these, the patient was described as being ‘violent, requires restraint’ (BARS category 7) in 806 (40%) episodes, ‘extremely or continuously active, not requiring restraint’ (BARS category 6) in 733 (37%), ‘signs of overt physical or verbal activity, calms down with instructions’ (BARS category 5) in 423 (21%), and ‘quiet and awake, normal level of activity’ (BARS category 4) in 29 (1%).

The most common categories of symptoms and behaviours noted to be present at the time of episodes of acute behavioural disturbance were patient distress (1323 episodes; 62%), followed by verbal aggression/aggressive behaviour (1009; 47%), overactive/boisterous behaviour (959; 45%), physical violence towards others (755; 36%), disorganised/chaotic/unpredictable behaviour (723; 34%), physical aggression towards property (637; 30%), the expression of paranoid, persecutory, grandiose or other delusional ideas/beliefs (517; 24%), thought disorder (420; 20%), behaviours suggesting the patient was actively hallucinating (337; 16%), and actual or attempted self-harm and/or risk of self-harm (327; 15%).

Which medications were administered?

The classes and combinations of classes of medication administered to manage episodes of acute behavioural disturbance are shown in Table 2.

With respect to oral medication, the most commonly used antipsychotics were haloperidol (*n*=217; 71% of administered antipsychotics), quetiapine (*n*=33, 11%) and olanzapine (*n*=23; 8%), and the most commonly prescribed oral benzodiazepine was lorazepam (*n*=809; 92%).

Where the parenteral route was used this was IM in 1079 of 1081 cases. The most commonly used IM antipsychotics were haloperidol (*n*=360; 66% of administered antipsychotics), aripiprazole (*n*=73, 14%), zuclopenthixol acetate (*n*=60; 11%) and olanzapine (*n*=47, 9%). Haloperidol was administered alone in 99 (19%) cases. The most common IM benzodiazepine was lorazepam (*n*=757, 99% of administered benzodiazepines). Of the 295 episodes in which a combination of an IM antipsychotic and IM benzodiazepine were used, the medications were haloperidol with lorazepam in 234 (79%). IM haloperidol was used in combination with IM promethazine in 30 cases.

Administration of high-dose antipsychotics

In 1756 (81%) episodes, the patient was prescribed antipsychotic medication to be taken regularly. Of the 542 episodes where parenteral antipsychotic medication was administered, the patient’s regular antipsychotic prescription was for a high dose in 51 (9%) cases. In a further 135 (25%) episodes, the administration of the additional antipsychotic medication for RT meant that the total dose for the day reached or exceeded the threshold for high dosage.

Is RT effective?

A pre- and post-RT behavioural activation rating was available for a subsample of 631 episodes for which parenteral medication was administered. In 25% of these episodes, the patient was reported as being ‘extremely or continuously active, not requiring restraint’ or ‘violent requires restraint’, in the hour following administration of RT (see Figure 1).

Are any demographic or clinical variables associated with route of medication administration?

With respect to males, univariable analyses revealed several factors associated with the route of administration of medication: the level of behavioural activation, age, ethnicity, a diagnosis of

Table 1. Demographic and clinical characteristics of the total national sample of 2172 episodes of acutely disturbed behaviour, and in the sub-groups where oral medication only (*n*=1091) or a regimen including parenteral medication (*n*=1081) was administered.

Key characteristics		Total episodes of disturbed behaviour *n*=2172 (%)	Episodes where oral medication only was administered *n*=1091 (%)	Episodes where parenteral medication was administered *n*=1081 (%)
Gender	Male	1196 (55)	690 (63)	506 (47)
	Female	976 (45)	401 (37)	575 (53)
Ethnicity	White/White British	1572 (72)	844 (77)	728 (67)
	Asian/Asian British	189 (9)	69 (6)	118 (11)
	Black/Black British	217 (10)	98 (9)	119 (11)
	Mixed or other	144 (7)	64 (6)	80 (7)
	Not stated/not collected/refused	52 (2)	16 (1)	36 (3)
Age bands	15–18 years	67 (3)	29 (2)	38 (4)
	19–25 years	431 (20)	195 (18)	236 (22)
	26–35 years	543 (25)	242 (22)	301 (28)
	36–45 years	361 (17)	201 (18)	160 (15)
	46–55 years	372 (17)	187 (17)	187 (17)
	56–65 years	178 (8)	61 (6)	117 (11)
	Over 65 years	220 (10)	176 (16)	44 (4)
Clinical psychiatric diagnoses	Organic disorder (F00–F09)	202 (9)	173 (16)	29 (3)
	Disorders due to psychoactive substance misuse (F10–F19)	265 (12)	134 (12)	131 (12)
	Schizophrenia spectrum disorder (F20–F29)	986 (45)	467 (43)	519 (48)
	Affective disorder (F30–F39)	449 (21)	195 (18)	254 (23)
	Personality disorder (F60–F69)	341 (16)	131 (12)	210 (19)
	Other psychiatric disorder(s)	535 (25)	178 (16)	155 (14)
	Diagnosis not yet ascertained	125 (6)	53 (5)	72 (7)
Legal status of patient	Detained in hospital under mental health legislation	1930 (89)	908 (83)	1022 (95)
	Informal patient	205 (9)	147 (13)	58 (5)
	Legal status unknown	37 (2)	36 (3)	1 (<1)
Clinical service providing care	Acute adult psychiatric ward	1455 (67)	733 (67)	722 (67)
	Psychiatric intensive care ward	444 (20)	185 (17)	259 (24)
	Low secure forensic/locked rehabilitation ward	149 (7)	111 (10)	38 (4)
	Medium and high secure forensic ward, including forensic learning disabilities services	124 (6)	62 (6)	62 (6)

Table 2. Medication administered for episodes of acute behavioural disturbance.

		Antipsychotic *n* (%)	Benzodiazepine *n* (%)	Promethazine *n* (%)
Episodes where oral medication only was administered (*n*=1091)[a]				
	Antipsychotic	120 (11)		
	Benzodiazepine	154 (14)	655 (60)	
	Promethazine	15 (1)	59 (5)	73 (7)
Episodes where parenteral medication was administered (*n*=1081)[b]				
	Antipsychotic	196 (18)		
	Benzodiazepine	295 (27)	423 (39)	
	Promethazine	44 (4)	42 (4)	74 (7)

[a]In 15 episodes a combination of an oral antipsychotic, oral benzodiazepine and oral promethazine was administered; [b]in seven episodes a combination of a parenteral antipsychotic, parenteral benzodiazepine and parenteral promethazine was administered.

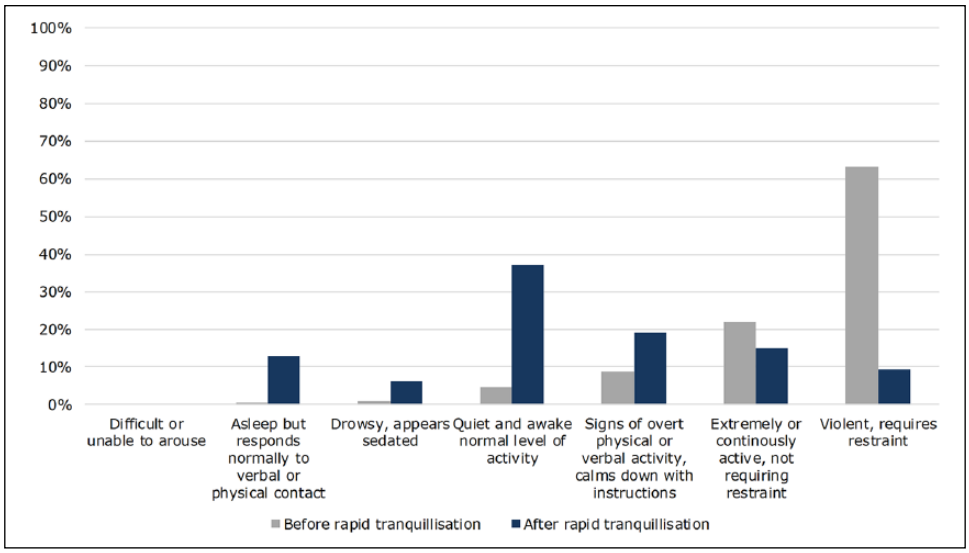

Figure 1. Level of behavioural activation before and after rapid tranquillisation where both pre- and post-recordings of behavioural activation were available (*n* of subsample=631).

dementia (F00–F09), schizophrenia (F20–F29), an affective disorder (F30–F39) or a personality disorder (F60–F69), being detained in hospital under mental health legislation, the type of clinical service providing care, being verbally aggressive, aggressive towards property or violent towards others, expressing paranoid ideas, the presence of thought disorder and displaying hallucinatory behaviour. All of these associations were statistically significant at a level of $p<0.05$. When entered into a multivariable model, only the level of behavioural activation, having a diagnosis of dementia or personality disorder, being detained in hospital under mental health legislation, the type of clinical service providing care, displaying overactive behaviour, physical violence towards others, and thought disorder remained statistically significant. The direction and strength of these associations can be seen in Table 3.

With respect to females, univariable analyses revealed that increasing levels of behavioural activation, ethnicity, a diagnosis of dementia (F00–F09), schizophrenia (F20–F29), an affective disorder (F30–F39) or a personality disorder (F60–F69), being detained in hospital under mental health legislation, displaying distress, being verbally aggressive, overactive, aggressive towards property or violent towards others, displaying disorganised/chaotic behaviour, and actual or attempted self-harm were associated with the administration of IM medication. When entered into a multivariable model, only the level of behavioural activation, age, a diagnosis of schizophrenia or an affective disorder, being detained in hospital under mental health legislation, appearing distressed, and actual or attempted self-harm remained statistically significant. The direction and strength of these associations can also be seen in Table 3.

Are any demographic or clinical variables associated with the choice of IM medication regimen? With respect to whether an IM benzodiazepine was administered alone or in combination with an IM antipsychotic, univariable analyses revealed that age, gender, ethnicity, a diagnosis of schizophrenia or personality disorder, the clinical service providing care, physical violence towards others, expressing paranoid ideas, thought disorder, hallucinatory behaviour and actual or attempted self-harm were all associated with regimen choice. Only four of these variables remained statistically significant in the multivariable model. These were as follows: (a) a patient's age – the odds ratio (OR) of receiving the combination was lower for those patients who were 15–18 years of age (0.32; 0.10–1.04, $p<0.001$) and over 65 years of age (0.32; 0.13–0.8, $p<0.001$) compared with the patients in the reference group, who were 26–35 years of age; (b) having a diagnosis of a personality disorder (OR 0.46; 0.30–0.71, $p<0.001$); (c) exhibiting physical violence towards others (OR 1.39; 1.00–1.92, $p=0.05$); and (d) displaying hallucinatory behaviour (OR 1.87; 1.21–2.89, $p=0.005$).

With respect to whether an IM antipsychotic was administered alone or in combination with an IM benzodiazepine, the univariable analyses revealed that the only statistically significant association was for disorganised/chaotic behaviour, where the OR of receiving the combination was 0.65 (0.45–0.93, $p=0.02$).

Discussion

As far as we are aware, this is the first large-scale study in the UK to describe the profile of psychiatric inpatients who have received psychotropic medicines for the management of acutely disturbed behaviour, and to explore how individual demographic and clinical variables are associated with both the route of administration and drug choice. The existing literature relating to rapid tranquillisation consists mostly of small audits and surveys that focus on adherence to guidelines, specifically post-RT monitoring. A major strength of our data is that they were obtained by local data collectors, soon after the episodes of disturbed behaviour, from clinical records and direct discussions with prescribers, and may therefore be considered more reliable than they would have been if derived retrospectively from clinical records alone.

Table 3. Multivariable analyses of the effect of potentially explanatory variables on the administration of parenteral rather than oral medication for episodes of acute behavioural disturbance in men and women.

Gender	Variable	Category	Adjusted odds ratio (95% CI)	*p*-Value
Males	Diagnosis of dementia (F00–F09)	No	1	<0.001
		Yes	0.11 (0.05–0.26)	
	Diagnosis of personality disorder	No	1	0.02
		Yes	2.00 (1.10–3.64)	
	Detained in hospital under mental health legislation	No	1	0.002
		Yes	2.52 (1.41–4.53)	
	Clinical service providing care	Acute adult	1	<0.001
		Psychiatric intensive care unit	1.14 (0.80,1.61)	
		Low secure	0.15 (0.08–0.28)	
		Medium or high secure	0.50 (0.28–0.92)	
	Overactive behaviour	No	1	0.01
		Yes	0.67 (0.49–0.92)	
	Physical violence towards others	No	1	<0.001
		Yes	1.74 (1.25–2.44)	
	Thought disorder	No	1	0.01
		Yes	1.58 (1.11–2.27)	
	BARS score[a]	-	2.63 (2.14–3.22)	<0.001
Females	Age (years)	26–35	1	<0.001
		15–18	0.39 (0.18–0.83)	
		19–25	0.68 (0.40–1.16)	
		36–45	0.36 (0.21–0.64)	
		46–55	0.41 (0.23–0.72)	
		56–65	0.94 (0.48–1.82)	
		Over 65	0.12 (0.08–0.22)	
	Diagnosis of schizophrenia (F20–F29)	No	1	<0.001
		Yes	2.17 (1.42–3.33)	
	Diagnosis of an affective disorder (F30–F39)	No	1	0.001
		Yes	2.12 (1.36–3.29)	
	Detained in hospital under mental health legislation	No	1	0.01
		Yes	2.16 (1.19–3.91)	
	Distress	No	1	0.04
		Yes	0.68 (0.47–0.98)	
	Actual/attempted self-harm	No	1	0.007
		Yes	1.87 (1.19–2.94)	
	BARS score[a]	-	2.25 (1.84–2.76)	<0.001

BARS: Behavioural Activity Rating Scale; CI: confidence interval.
[a]The odds ratios stated represent the chance of receiving intramuscular medication for each one point increase in the BARS score.

Who received medication for acute behavioural disturbance in psychiatric inpatient settings?

In the vast majority of episodes of acutely disturbed behaviour, the patient was detained in hospital under mental health legislation and occupied an acute adult or psychiatric intensive care bed. More than half of all the episodes occurred in males, and in almost half, the patient was 35 years of age or younger. Two-thirds of episodes occurred in patients with a schizophrenia spectrum disorder (ICD10 F20–F29) or affective disorder (ICD10 F30–F39). These diagnostic findings are consistent with those of older, relatively small-scale, local clinical audits (Geffen et al., 2001; Pilowsky et al., 1992). More than one in 10 episodes involved a patient with a substance misuse disorder (ICD10 F10–F19); active substance misuse is known to be strongly associated with violence and aggression (Fazel et al., 2009; Friedman, 2006). Further, more than one in seven episodes involved a patient with a personality disorder (ICD10 F60–F69).

Which oral medications are used?

A benzodiazepine (predominantly lorazepam) was used in the vast majority of cases where oral medication was administered and for three out of every five episodes this was as monotherapy. In contrast, an antipsychotic medication alone (mostly haloperidol) was

used in only one in 10 episodes. The use of other benzodiazepine and antipsychotic medications was minimal.

The guideline for the management of violence (National Institute for Health and Care Excellence, 2015) refers to the use of medication as part of an individualised clinical management plan to decrease the risk of violence or aggression and as part of a de-escalation strategy but does not specify which medications should be used in these situations. The guideline draws attention to the lack of good quality evidence to support such a recommendation and identifies studies to address this area of clinical practice as a research priority. There is very limited evidence to support the use of oral lorazepam, albeit combined with an oral antipsychotic (Currier et al., 2004), or oral haloperidol combined with an oral benzodiazepine (Barbee et al., 1992), so the finding that these two medicines are used in such a high proportion of cases likely reflects accepted and conventional practice and suggests that clinicians may extrapolate from their clinical experience of using these medicines for behavioural disturbance in their parenteral formulations. It may also reflect that clinical guidelines for treating acute behavioural disturbance tend to recommend these medicines in their parenteral formulations (National Institute for Health and Care Excellence, 2015). Thus, the choice of oral lorazepam or oral haloperidol may be influenced by the notion that if this oral treatment were to fail, the same medications would be appropriate by the parenteral route, thus minimising a patient's exposure to different psychotropic medicines

Which parenteral medications are used?

The gold standard for RT has not yet been determined but recent guidance recommended the use of either IM lorazepam on its own or IM haloperidol combined with IM promethazine in adults (National Institute for Health and Care Excellence, 2015). Our data reveal that practice in UK inpatient psychiatric settings is not wholly consistent with this recommendation; where an IM benzodiazepine was administered, lorazepam was chosen in almost all cases and where an IM antipsychotic was administered, this was haloperidol in two-thirds of cases, but when an antipsychotic was combined with a sedative, lorazepam rather than promethazine was chosen in four-fifths of cases. The efficacy and safety of this combination are supported by a small randomised controlled trial (RCT) conducted in a psychiatric setting (Battaglia et al., 1997) that compared haloperidol 5 mg IM, lorazepam 2 mg IM and a combination of haloperidol 5 mg IM and lorazepam 2 mg IM for 'psychotic agitation'. The combination was more effective than either drug alone, in that fewer additional injections were required, and safer than haloperidol alone, which was associated with more extrapyramidal side effects (EPSs). However, reviewing the relevant evidence, a Cochrane systematic review (Powney et al., 2012) concluded that while there was no strong evidence that adding a benzodiazepine to haloperidol was beneficial for psychosis-induced agitation, it carried a risk of additional harm.

Our findings suggest that UK clinicians are commonly using combinations of medicines for RT that have become custom and practice, despite a lack of robust supportive evidence, and tend not to use the combination recommended by the National Institute for Health and Care Excellence, of which they may have little clinical experience.

The Cochrane systematic review mentioned above (Powney et al., 2012) addressed the efficacy and safety of haloperidol, administered by any route, for psychosis-induced aggression or agitation and drew attention to the propensity of haloperidol, when given alone, to cause acute EPSs. These authors concluded that 'where additional drugs to offset the adverse effects are available, sole use of haloperidol for the extreme emergency, in situations of coercion, could be considered unethical' (page 1). Nevertheless, in almost one in 10 of the episodes of disturbed behaviour in our sample for which an IM antipsychotic was used, haloperidol was administered on its own. This suggests that not all UK clinicians may be aware of, or agree with, the conclusions of the Cochrane review. An alternative explanation is that some prescriptions may have been written in a way that allowed the nurse administering the RT medication to choose to give haloperidol alone rather than as part of an intended combination.

What influences the route of administration?

In both men and women, greater levels of behavioural activity and detention in hospital under mental health legislation were associated with a greater likelihood of medication being administered by the parenteral route. These associations are clinically plausible in that a decrease in a patient's ability to self-regulate and cooperate with staff to keep themselves and others safe is likely to prompt increasingly restrictive interventions. However, the clinical profile of men and women who received parenteral medication differed in several ways. With respect to men, having a diagnosis of personality disorder, being cared for on a psychiatric intensive care unit, displaying physical violence towards others and exhibiting thought disorder were strongly associated with receiving parenteral medication. Taken together, these factors suggest that men tend to receive parenteral medication to keep others safe. With respect to women however, having a diagnosis of schizophrenia or an affective disorder and concerns about actual or attempted self-harm were associated with receiving parenteral medication, suggesting that women tend to receive medication by this route to keep themselves safe. Initiatives to reduce the use of RT in routine clinical care may need to consider gender. For example, services that care for men may particularly benefit from allowing patients time for reflection in a physical space away from others, while services that care for women might consider prioritising the provision of appropriate psychological interventions for issues such as coping with psychotic symptoms and thoughts of self-harm.

What influences choice of medication regimen?

Our multivariable regression analyses revealed that an antipsychotic medication is likely to be added to a benzodiazepine when a patient is physically violent towards others. Persistent aggression and violent behaviour in people with schizophrenia may have a heterogeneous aetiology (Volavka and Citrome, 2008) and this is likely to hold true over a wide range of psychiatric disorders during both acute episodes of illness and periods of at least partial symptom-stability; underlying causes include response to psychotic symptoms, co-morbid substance misuse and/or personality disorder features, affective instability, impulse control disorders and simple

frustration at not feeling listened to or having boundaries imposed. Volavka and Citrome (2008) argue eloquently that the optimal pharmacological treatment of aggressive behaviour may be dependent on the nature of the driver for that behaviour. However, studies that address the efficacy and tolerability of pharmacological strategies to treat aggression do not selectively recruit patient samples based on the perceived aetiology of the behaviour. Thus, the proportions of patients with any given driver for their disturbed behaviour are likely to differ across drug treatment studies, which may well affect the likelihood of identifying selective anti-aggressive efficacy. While this is a credible hypothesis, there is no objective evidence to date to support symptom or diagnosis-driven pharmacological strategies for managing either acutely or chronically disturbed behaviour. In clinical practice however, our findings show that those patients who are physically violent are more likely than those who are not to receive an antipsychotic medication in combination with a benzodiazepine, and this may reflect the accepted practice in UK settings of prescribing the so-called '5&2' regimen (referring to haloperidol 5 mg and lorazepam 2 mg), in high-risk clinical situations. There are no randomised studies that directly compare the effectiveness of the National Institute for Health and Care Excellence-recommended combination of haloperidol and promethazine for RT with the combination of haloperidol and lorazepam commonly used in clinical practice. The relative utility of these two regimens is therefore unknown and a head-to-head study is warranted.

The multivariable regression analyses also revealed that patients with a diagnosis of personality disorder and those in their mid-teens (younger than 18 years of age) or elderly (older than 65 years) were more likely to receive a parenteral benzodiazepine alone. This is in keeping with guideline recommendations for the treatment of personality disorder (National Institute for Health and Care Excellence, 2009) and may also reflect awareness that antipsychotic medication can be associated with a significant side-effect burden in both the very young (Correll, 2011) and older adults (Masand, 2000). None of the demographic or clinical variables collected were associated with increased odds of a benzodiazepine being added to an antipsychotic, and disorganised/chaotic behaviour was the only clinical feature that was more likely to be treated with an antipsychotic alone.

Does RT result in exposure to high-dose antipsychotic medication? In the UK, guidelines (National Institute for Health and Care Excellence, 2015) recommend taking a number of factors into account when selecting medication for RT; one such factor is the total daily dose of regularly prescribed medications. Our UK findings were that in almost one episode in 10 where antipsychotic medication for RT was administered, the patient was already prescribed regular, high-dose antipsychotic medication. Administration of the RT regimen resulted in the total antipsychotic dose for that day reaching or exceeding the high-dose threshold in a further one in four cases. However, there are no systematically collected data that allow assessment of the efficacy and safety of such transient high dosage. This may be partly because recruitment to the RCTs of RT that have informed evidence-based guidelines has been largely restricted to patients who presented as a psychiatric emergency and were either known to be receiving RT as their only antipsychotic medication or were unlikely to be taking regular antipsychotic medication (Alexander et al., 2004; Huf et al., 2007; Raveendran et al., 2007; TREC Collaborative Group, 2003).

The calming and sedating effects of antipsychotic medication are central to their use for RT. However, a prospective observational study suggests that that there may be a tipping point at which additional sedation becomes unsafe (Calver et al., 2013). This study found that where high-dose sedation (defined as initial IM doses of haloperidol, droperidol or midazolam of higher than 10 mg), was used to manage episodes of acute behavioural disturbance in a psychiatric inpatient setting, this did not result in more rapid or effective sedation but was associated with double the incidence of side effects seen with standard doses, specifically hypotension and oxygen desaturation. Indeed, most subjectively unpleasant and/or potentially serious side effects of antipsychotics are dose-related, including acute EPSs (Geddes et al., 2000), neuroleptic malignant syndrome (Oruch et al., 2017) and seizures (Pisani et al., 2002). Further, patients who are acutely behaviourally disturbed are more likely than the general population to have electrolyte disturbances and high levels of circulating catecholamines, both of which are risk factors for cardiac arrhythmias; the arrhythmogenic risk associated with antipsychotic medication is generally considered to be dose-related (Reilly et al., 2000).

The vast majority of patients who received RT in our study were prescribed antipsychotic medication to be taken regularly and it is likely that, for most, steady state plasma levels had been achieved. An additional single dose of an antipsychotic could be expected to increase the risk of dose-related side effects in the short-term immediately after administration; such an effect was noted in a small observational study that explored the use of PRN medication in hospitalised patients with psychosis (Geffen et al., 2001). Individual patients may of course receive multiple additional doses of antipsychotic medication over varying timeframes, and whether the fluctuating plasma levels and transient exposure to high-dose antipsychotics associated with this treatment strategy have any clinical consequences in the long-term requires further investigation.

How effective is RT?

The data from a subsample of episodes, selected because relevant information on the outcome of RT was available, revealed that in the hour after administration, the patient was calm or asleep in almost three out of five episodes. However, for one episode in four, the patient's level of behavioural activation was described as at least 'extremely or continuously active'. Thus, RT could be considered to have failed to achieve calmness or a tranquil state in these cases. This is consistent with the findings relating to early response reported in the TREC studies with IM lorazepam (Alexander et al., 2004) or a combination of IM haloperidol and IM promethazine (Huf et al., 2007).

With respect to IM preparations of antipsychotic medication, there is limited information on the effectiveness of second-generation antipsychotics in clinical emergencies (Baldacara et al., 2011; Kishi et al., 2015). A review of RCTs (most of which were placebo-controlled licensing studies) testing parenteral formulations of second-generation antipsychotics for psychotic agitation concluded that, for 'response at two hours' the numbers needed to treat were three for olanzapine, four for haloperidol and five for aripiprazole (Citrome, 2007). Thus, even in those patients who

were less behaviourally disturbed than our clinical sample and who were sufficiently co-operative to give informed consent to participate in these studies, a single injection of a second-generation antipsychotic medication did not lead to the desired outcome in the majority of patients.

Where initial pharmacological efforts to induce a state of calm fail, there is very limited evidence on which to base recommendations for further interventions. All antipsychotic medications used in RT (or their active metabolites) have half-lives of 20 h or more (Electronic Medicines Compendium, 2018). Frequent administration could lead to accumulation that would place the patient at an increased risk of serious adverse effects.

Significant outcomes

1. In the context of the emergency treatment of acutely disturbed behaviour, the use of parenteral rather than oral medication reflected different target behaviours in men and women. Initiatives to reduce the need for, and therefore use of, rapid tranquilisation may be more successful if they are gender-specific, for example, targeting self-harm in women and violence towards others in men.
2. Where behavioural disturbance involves violence towards others, a combination of parenteral haloperidol and lorazepam is most often used rather than the combination of haloperidol and promethazine recommended in UK clinical guidelines. A head-to-head randomised clinical trial comparing these regimens is warranted.
3. The initial attempt to manage acutely disturbed behaviour with parenteral medication may fail to achieve a calming effect in up to one in four episodes. There is very limited evidence on which to base the choice of next-step pharmacological strategies.

Limitations

1. Our findings relate only to episodes of acutely disturbed behaviour that occurred in mental health settings and may not be generalisable to other clinical settings, such as accident and emergency services.
2. While we describe the symptoms and behaviours present at the time that medication was administered for an episode of acutely disturbed behaviour; the extent to which any of these particular symptoms or behaviours may be considered to be directly related to the decision to administer medication remains a matter of conjecture.
3. We did not collect information on patients' psychiatric or medical history and so were unable to explore whether factors such as a history of serious violence or current physical co-morbidity influenced the choice of medication route or regimen for an episode of acutely disturbed behaviour.

Acknowledgements

The work of the POMH-UK is funded solely by the NHS mental health trusts and other healthcare organisations that participate in POMH-UK national quality improvement programmes. Acknowledgements are due to the POMH-UK leads in all participating healthcare organisations and the clinicians and clinical audit staff who collected and submitted the audit data. Thanks are also due to the following members of the POMH-UK team: Krysia Zalewska and Susan Lemmey. Statistical analyses were conducted by Paul Bassett, an independent statistician (www.statsconsultancy.co.uk).

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CP, CA, SD, CO and EF have nothing to declare. TREB has been a member of scientific advisory boards for Sunovion, Otsuka/Lundbeck and Newron Pharmaceuticals and received speaker fees from Janssen.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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