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TREC-LEBANON – RAPID TRANQUILISATION OF AGGRESSIVE PATIENTS IN THE EMERGENCY PSYCHIATRY SETTING

By

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"A dead thing goes with the stream, but only a living thing can go against it." – G.K. Chesterton

Abstract

Violent or aggressive episodes are particularly prevalent in the emergency psychiatric settings (10%) often as a consequence to a variety of disorders ranging from the organic to mental disorders (i.e. Schizophrenia, Substance Use, etc.). While guidelines state patients should be calm in order to attain a diagnostic history, physical and laboratory tests before treatment is to be started, the violent episode presented often makes it impossible – ruining necessary history, physical and laboratory work as well as placing both staff and patients in a potentially harmful state. With this, rapid tranquilisation becomes both necessary and unavoidable. This thesis, the first of its kind in Lebanon and the Middle East, undergoes a pragmatic randomised controlled trial in Lebanon's only public psychiatry hospital. I begin with systematically defining 'what is aggression' specifically within the psychiatry emergency setting and the common disorders associated with it. I then conducted a systematic literature review of all known surveys examining both clinicians' opinions and practice on how aggressive episodes are treated. Following the survey of surveys, I proceeded to conduct a survey of both clinicians' opinions and what happens in practice in Lebanon's Psychiatric Hospital of the Cross. With the results and assistance from Cochrane Library, I conducted a systematic overview and

updated reviews - both direct and indirect. While results did show a variety of treatments used in Lebanon have been tested in trials, Lebanon's main SOS treatment – the 'HPC' treatment has never been investigated within a trial and no reviews exist, although there is evidence it is used in practice. With this, I designed the trial protocol suited for Lebanese practice and with the University of Nottingham's ethics board and representatives of the Lebanese hospital, the trial commenced and ran to completion over a period of 10 months. A total of 100 patients were randomised with 48 in the HP group and 52 in the HPC group. Primary measures of outcomes were calm or tranquil at 20 minutes. Results showed no significant differences between both interventions with confidence intervals showing a slight preference towards the triple therapy when sampling size is adjusted. The thesis concludes with the difficulties of running such a trial within the region and the practical solutions to each problem presented.

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Overview

Introduction

Aggression, agitation and violence are common behaviours seen in healthcare settings and particularly in the psychiatric emergency. Despite efforts to avoid escalation, then de-escalation, around one in ten patients displaying aggression are given drugs to rapidly calm their mental state.

Guidelines recommend that patients should be calm and tranquil in order for an accurate diagnostic history and other investigations to be taken before any form of pharmacological treatment is implemented. Aggression and violence make this impossible and, at best, leads to histories being rushed and fragmented, diagnoses speculative and the physical examination incomplete. Guidelines recommend as a prerequisite of good clinical care, every effort should be made to avoid aggression and, should it occur, defusing techniques should be employed to offset any escalation of the episode.

However, avoidance often fails, and de-escalation commonly may not have the desired effect. Every violent episode is a result of multiple failures but, at this far from ideal point, to ensure the safety of everyone involved, rapid tranquilisation becomes unavoidable. This thesis focuses on this point – when all else has failed.

Exactly which drug, or combination of drugs, is best for the purpose of rapid tranquilisation is still a matter of debate. High-profile consensus guidelines, such as USA's APA guidance and UK's NICE allow for several recommendations of medications including one [correctly] deemed unethical by other parts of the world. The Middle East and specifically Lebanon have no guidance. Furthermore, there remains a number of guidelines that have not updated their recommendations from present trials.

Good evidence on the comparative effects of any drugs used for rapid tranquilisation is rare. Few places have fairly tested the medications used locally in their local setting. The UK, USA, Australia and Canada have all never randomised their own recommended treatments in their local health care settings.

Aim

The aim of this work is to investigate the approaches taken to rapid tranquilisation of people in psychiatric emergencies in Lebanon.

Objectives

The objectives of this thesis were to

- Explore, specifically for Lebanon, concepts and causes of aggression and violence in psychiatric settings. This

- was successfully done by conducting a survey in the Lebanese psychiatry setting, using lessons and improving methodological quality of past surveys that addressed this topic in their respective environment.
- *Systematically* identify surveys of what people were actually using in clinical care for managing acute aggressive episodes [investigating if it was already known what occurs in Middle East practice] which was successfully done in a systematic review of relevant surveys and an incursion into bioinformatics that highlighted no survey of clinicians' opinion or management existed in the Middle East.
- Due to the lack of evidence, a survey of treatments was conducted in the Lebanese aggressive psychiatric setting.
- *Systematically* investigate existing trial evidence for the treatments relevant to the practice in Beirut [to identify if there were gaps in this evidence]. This was successfully done by conducting a systematic overview of relevant based trials that highlighted no reviews or trials existed for the Lebanese SOS treatment of haloperidol plus promethazine plus chlorpromazine.
- [Since gaps were apparent] a protocol was designed with local that was acceptable to them, of direct

relevance to people in Lebanon which was successfully completed, registered and published.

- Successfully conducted and completed 'TREC – Lebanon' which is the first randomised controlled trial of patients displaying an aggressive episode in the Lebanese psychiatry emergency setting.

Chapter synopses

Chapter I

This sets the theme for this thesis with a broad literature review on aggression, agitation and violence including their definitions, their prevalence in healthcare settings, aetiology, policy and management. It begins with defining what are aggression, agitation and violence and attempts to do this in a semi-systematic way. While aggression, agitation and violence are universally prevalent, the starting and endpoint varies across cultures. For example, verbal abuse can be considered aggressive in one culture whereas another culture only deems physical acts as aggressive. To satisfy these differences in order to formulate an encompassing all usable definition, I proceeded to locate different works that defined aggression in the healthcare setting – taking each author's unique characterisation and integrating it into a workable overall definition. The second part focused on aetiological aspects of

aggression in the healthcare settings that included both general and psychiatric hospitals and what is meant by 'the emergency psychiatry setting'. Moreover, it lists the common psychiatric disorders associated with aggression specifically but not limited to the psychiatric emergency setting. Finally, the review of Chapter I ends with management of aggression in the psychiatric emergency setting including an overview of all steps that happen *before* rapid tranquilisation becomes an option. It addresses the differences in policies between Lebanese practice (none) and UK practice (NICE) on how aggression in the psychiatric emergency setting is approached.

Chapter II

To find out what are the treatments used in front-line care for rapid tranquilisation across the world I undertook a systematic review of surveys of treatment of patients who are at risk of an aggressive episode in the psychiatric emergency. In trying to avoid the biases associated with a less than systematic approach, I found myself drawn into bioinformatics. So, at the start of this chapter, I present important and, I think, unique evidence showing how undertaking a *systematic* review of this type of methodology is probably impossible.

I did locate several surveys (and one important audit). The second section of Chapter II critically appraises these and

highlights diversity of opinion and practice. There were no surveys of practice in the Middle East.

Chapter III

Chapter III describes the Lebanese survey. As no survey of practice involved anywhere near Lebanon there was a strong argument to really find out what was happening in frontline care in Beirut. Additionally, a survey is a prerequisite to any truly pragmatic trial, as the latter type of study should run with minimal disruption to standard care – and for that to happen - standard care must be intimately understood.

In this chapter, I describe the survey I conducted in Lebanon's largest psychiatric hospital. I tried to learn from the best surveys of the past but kept it simple to ensure success. The opinions of Lebanese clinicians of how rapid tranquilisation should be undertaken match those of other clinicians across the globe; avoid if possible, de-escalate if not and only as a last resort use rapid tranquilisation. The choices of what is used for rapid tranquilisation varied but this hospital's preferred first-line treatment that was a combination of haloperidol plus promethazine plus chlorpromazine (HPC). Finally, the survey granted me the opportunity to build working relationships with everyone who were to be involved

in later stages of this work. This chapter is now a published paper.

Chapter IV

Having discovered the preferred treatments for Beirut, the next logical step was to investigate the best evidence of their effects by a systematic overview of relevant reviews of trials. In this chapter, I report an overview of all relevant reviews and trials pertaining to interventions used in rapid tranquilisation in Lebanese psychiatric practice. The relevant negative finding was that no *reviews* existed for Lebanon's preferred emergency treatment (HPC), and, digging deeper, I found no *randomised [or non-randomised] trials* either. The HPC combination clearly worked or it would not have lasted in clinical practice – but its comparative effectiveness had not been tested in trials. This work supported randomisation of the HPC treatment with the possibility of seeing if a simpler medication approach would suffice. Why use three medications at once if less would do?

Chapter V

In this chapter, I describe the process of creating a protocol for a pragmatic randomised trial in the psychiatric emergency setting in Beirut. While I present the chapter mainly in manuscript form, an overview of the methods of its creation

(actions that happened really between Chapter IV and V) are also reported. This included numerous meetings between me and the University of Nottingham Ethics Board and myself and the staff at the Psychiatric Hospital of the Cross, Beirut. The round table meetings at the hospital decided on important trial details such as who should participate, how long can the trial run for, interventions to be used and the outcomes of importance. The protocol of the trial (TREC-Lebanon) was, thus, designed according to the requests of both institutions and then registered and fully published before first randomisation.

Chapter VI

Here I report the TREC-Lebanon trial with both primary and secondary results and their implications for practice and research.

Chapter VII

In this concluding chapter I summarise the work but discuss particular problems encountered in its conduct and how they were managed (i.e. ethics, conduct, funding), what there is to learn from the work, its immediate implications and give some directions for future research and practice.

1. Chapter I – Aggression in Psychiatry

1.1 Introduction

Chapter I examines general issues of aggression in psychiatry, it attempts to draw together broad definitions and understandings of generally accepted views of what aggression/agitation/violence is in the context of psychiatric care and its prevalence in care settings. The chapter ends with a consideration of the psychiatric disorders most associated with aggressive behaviour and outlines broad approaches to treatment.

1.1.1 What is aggression?

'Aggression' as a term has been used interchangeably with other synonyms such as agitation and violence. Aggression is a deliberate behaviour with the sole purpose of inflicting physical damage to persons or property – as well as animals (Vitiello & Stoff, 1997). More specifically, aggression has been defined as *any progression of behaviour* to which the end goal is the injury of the individual to whom it is directed (Dollard, Miller, Doob, Mowrer, & Sears, 1939). Furthermore, although it is emphasised that the role of intention defines aggression, most psychologists agree that it is *actual observable behaviour* causing harm that best defines aggression (Anderson & Bushman, 2002). In his book, '*Aggression: Its Causes,*

Consequences, and Control', Berkowitz (1993) defined aggression as *goal oriented motor behaviour* that has a deliberate intent to harm or injure another person or object. This definition includes both physical and verbal acts of aggression. To try to solve the problem of multiple authors defining aggression, agitation and violence in different ways, I formulated tables containing the key definitions and categorised variables within these definitions (See Table 1.1: Definition of aggression).

Table 1.1: Definition of aggression

			Variables							
Year	**Author**	**Definition**	**Intention**	**Behaviour**	**Time**	**Animate being**	**Object**	**Injury**	**Goal oriented**	**Observable**
1939	Dollard et al.	- Any progression of behaviour to which the end goal is the injury of the individual to whom it is directed.		✓	✓	✓		✓	✓	
1961	Buss	- A response that delivers noxious stimuli to another organism.		✓		✓		✓		
1989	Berkowitz	- Any form of behaviour directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment.		✓		✓		✓	✓	
1991	Dodge	- Behaviour deliberately aimed at harming people and/or objects	✓	✓		✓	✓	✓		
1997	Vitiello & Stoff	- Behaviour deliberately aimed at inflicting physical damage to persons or property.	✓	✓		✓	✓	✓		
2004	Baron & Richardson	- Any form of behaviour directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment.		✓		✓		✓	✓	
2008	Zirpoli	- The observable manifestation of aggression, which is defined as any act intended to cause harm, pain or injury in another person.	✓	✓		✓		✓		✓
2012	Liu, Lewis, & Evans	- A broader construct that includes physical, verbal, psychological and other means of causing harm.		✓				✓		

People can harm others/animals/objects in a multitude of ways, and it is useful to distinguish between different forms/acts of aggression. For example, *physical aggression* is harm caused by hitting, biting, kicking, clubbing, stabbing and shooting. *Verbal aggression* causes harm using words such as yelling, screaming, swearing and name calling – or causing harm to someone's reputation or friendship through what is said to others verbally (or digitally) in what is called *relational aggression* (Craig & Huesmann, 2003).

Aggression can be either *direct* with the victim being physically present or *indirect* whereby the victim is not present – such as destroying someone's property or spreading rumours about them. Aggression differs in terms of function. It may comprise of intent to hurt the individual, as in reacting aggressively to being provoked (i.e. affective, hostile, impulsive, reactive or retaliatory aggression) or it may comprise of a well-considered and deliberate plan to harm an individual to attain a desired goal (i.e. proactive, planned, cold aggression or instrumental). Aggression can be an automatic innate response for self-preservation (i.e. fight or flight) or may involve a scheme for aggressive behaviour that is enacted multiple times that the response is no longer thought through. These distinctions are problematic in the sense that events can occur that do not fit the categories described above. However, a viable approach in

understanding aggression is to consider aggressive actions on three levels:

- The degree where the goal is to harm the victim versus benefit the perpetrator;
- The level of aggressive emotion that is present; and
- The degree to which the aggressive act was planned (Craig & Huesmann, 2003).

This thesis primarily addresses aggression in the emergency setting. The majority of the characteristics noted above are applicable and all vary based on both the caretaker and the patient involved. For example, direct and indirect aggressions are common in the psychiatric emergency setting. Relational aggression could be real (i.e. patient spreading rumours about the clinician or patient breaking the clinician's chair when not around, etc.). No studies were identified that have investigated the impact of relational aggression in the emergency psychiatric setting. Since this literature is concerned with emergency psychiatry, whereby the 'emergency' is a serious event requiring immediate action, relational aggression does not apply readily within this framework. Direct and indirect aggression are threats that could cause *immediate* harm – although it could be argued that indirect aggression such as verbal aggression does not cause immediate harm. However, clinicians should not take

verbal aggression lightly in the same manner clinicians do not take suicide threats from patients lightly and proceed to address the situation. Finally, the literature addressing aggression in psychiatry has shown a general consensus agreeing to Berkowitz's definition of aggression (Jones et al., 2011). The final result adding Berkowitz's and other authors' common variables define aggression as:

'*The observable progressive behaviour with the goal of causing harm whether physical or psychological towards another organism or object – while the person is motivated to escape, avoid or diminish such action*'.

1.1.2 What is agitation?

There seems to be even less consensus on what constitutes 'agitation' with little agreement on which behaviours and/or cognitive states would best define it (Fugate et al., 1997). Descriptions range from constant uninhibited movements to violent displays of aggression and rage. Some definitions are limited to only motor behaviour or a combination of both motor and verbal behaviour without involving cognitive symptoms such as reduced attention, confusion or disorientation. Authors agree that a common definition for agitation is important for clear understanding among researchers but consensus seems difficult to arrive at (Love,

1992). Once again, using the same technique as above, key definitions across time were identified and a table formulated to bring these together (See Table 1.2: Definition of agitation). For the purpose of this thesis, agitation is defined as *'a state of disturbance that comprises of either verbal or/and motor restlessness'*.

Table 1.2: Definition of agitation

			Variables				
Year	**Author**	**Definition**	**State**	**Restlessness**	**Disturbance**	**Motor**	**Verbal**
1877	Johnson	- The state of being moved or agitated; as the waters, after a storm, are sometime in violent agitation.	✓				
1967	Linn	- Physical excitement and restlessness that is usually but not necessarily associated with mental distress or disturbance.		✓	✓		
1978	Critchley & Arthur Salusbury	- Mental disturbance that causes the motor restlessness.	✓		✓	✓	
1989	Gelder, Gath, & Mayou	- A state of restlessness which is experienced by the patient as inability to relax and is seen by an observer as restless activity	✓	✓			
1993	Kendell	- agitated subjects usually feel anxious or tense and this feeling is usually transmitted to the observer, but agitation is a description of behaviour not of mood.	✓				
1996	Campbell	- A state of tension or restlessness as a whole that includes both mental and physical components.	✓	✓		✓	✓
1998	Verma, Davidoff, & Kambhampati	- Verbal or motor activity that poses a risk to the safety of the patient or caregiver, impedes the process of caregiving or impairs the patient's functioning.				✓	✓
2000	Allen	- The diagnostic counterpart of RT: a temporary disruption of the typical physician-patient collaboration, which interferes with assessment and treatment during a period when immediate assessment and treatment are needed.	✓				
2000	Lindenmayer	- Comprises verbal and physical, aggression and non-aggressive components: motor restlessness, heightened responsivity to internal and external stimuli, irritability, inappropriate or purposeless verbal or motor activity – including vegetative signs and an unstable course.	✓	✓		✓	✓

1.1.3 What is violence?

The World Health Organisation (WHO) defines violence 'as 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 or psychological harm, mal-development or deprivation' (World Health Organization, 1996). WHO divided violence into three categories: self-inflicted, interpersonal and collective (See Table 1.3: Parameters of violence). Moreover, each category is further subdivided to convey specific types of violence as well as the settings and nature of the violent displays (sexual, physical, neglect, deprivation or psychological). Finally, using the same technique, definitions of violence tabulated (See Table 1.3: Parameters of violence) and for the purpose of this thesis, violence is defined as '*an expression of many forms including verbal or physical patterns with differential targets, such as outward violence toward property and other persons, and inward violence toward the self' (See* Table 1.4: Definitions of violence*).*

Table 1.3: Parameters of violence

			Physical	Sexual	Psychological	Deprivation
Self-inflicted	Suicidal behaviour		✓		✓	✓
	Self-abuse		✓		✓	✓
Interpersonal	Family/partner	Child	✓	✓	✓	✓
		Partner	✓	✓	✓	✓
		Elder	✓	✓	✓	✓
	Community	Acquaintance	✓	✓	✓	✓
		Stranger	✓	✓	✓	✓
Collective	Social		✓	✓	✓	✓
	Political		✓	✓	✓	✓
	Economical		✓	✓	✓	✓

Table 1.4: Definitions of violence

			Variables						
Year	**Author**	**Definition**	**Behaviour**	**Action**	**Physical**	**Verbal**	**Person**	**Object**	**Self**
1972	Hagen, Mikolajcza, & Wright	- The entire spectrum of assertive, intrusive or attacking behaviour directed at the self, others, or property.	✓	✓			✓	✓	✓
1982	Bouras, Trauer, & Watson	- Verbal abuse and threatening behaviour.	✓			✓			
1990	James, Fineberg, Shah, & Priest	- Any act of actual physical aggression involving physical contact, irrespective of outcome.		✓	✓				
2002	World Health Organization	- 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.	✓		✓		✓		✓
2008	Volavka & Citrome	- Can be expressed in many forms including verbal or physical patterns with differential targets, such as outward violence toward property and other persons, and inward violence toward the self.	✓	✓	✓	✓	✓	✓	✓

1.2 Aggression/violence in care settings

1.2.1 General hospitals

Aggression and violence are common in hospitals. Up to half of people who work in healthcare (doctors, nurses, technicians, etc.) experienced some form of violence during their careers (Al-Sahlawi, Zahid, Shahid, Hatim, & Al-Bader, 1999; Schulte, Nolt, Williams, Spinks, & Hellsten, 1998). A survey of 65 Emergency Room (ER) departments in the USA reported 3461 physical attacks occurred over a 5-year period (Kansagra et al., 2008). Weapons (guns and knives) were present at the ER on almost a daily basis. Violence in the ER is not limited to the USA. Australia and Turkey report similar rates (Boz et al., 2006; Crilly, Chaboyer, & Creedy, 2004). The UK's first prospective study of its kind researchers defined an aggressive episode as a verbal threat or physical violence (Morgan & Steedman, 1985). Their results showed 51 episodes of physical violence in a sample of 109 offenders over a 6-month period. Following this, the Health Services Advisory Committee surveyed 5000 workers in various healthcare districts (60% response rate) with 21% of staff reported having an injury due to physical assault by a patient in the past year (Saines, 1999). In another study, in Bristol Royal Infirmary, over a 10-year period there were 407 reported incidents with staff experiencing episodes ranging from punching, kicking,

slapping, grabbing, head butting - as recorded in the violent incident record book of security workers at the Infirmary (Cembrowicz & Shepherd, 1992). In Canada, 51% of staff that responded to emergency psychiatric admissions had experienced physical violence (Fernandes et al., 1999). In New Zealand, the rates were higher with 75% of the respondents citing they had experienced physical aggression in the past 3 months (Lee, 2001).

1.2.2 Psychiatry settings

Aggression within psychiatric wards is prevalent in comparison to general health care settings (Rippon, 2000). This is due to violent behaviour having a higher risk ratio with patients who have a history of psychiatric problems (Fazel & Grann, 2006). People with aggressive/agitated/violent behaviour may be taken to a place of psychiatric care – even if their problem is erroneously considered to be due to psychiatric disorder. Whether or not the root cause is mental illness, it is probable that staff in a psychiatric unit will still have to deal with the problematic behaviour.

Depending on the level of service, psychiatric care can be a sophisticated network of sites of care offering different levels of support operating under a medical/social/psychological multidisciplinary model to the most rudimentary of services in

low/middle income countries (Patel et al., 2007; Saraceno et al., 2007). In high-income country services care can be fragmented and far from ideal but emergency services may operate though a specialist Crisis Team service, perhaps employing Emergency Rooms – either general or specific for psychiatry – for the point of entry to specialist services for the aggressive patient.

Box 1.1: Definition of emergency in psychiatry setting

Definition

Within the context of this thesis, an emergency psychiatry setting is *any* healthcare setting whereby healthcare professionals urgently treat people suffering from any psychiatric disorder. In this case, the treatment is the management of acute aggression/violence.

In any event, psychiatric staff, or more generally trained staff who are considered to have some responsibility for provision of care to people who are at risk for an aggressive episode, may be called upon to manage people who present with agitation, aggression or even violence. Levels of training vary enormously (Daffern & Howells, 2002) as do culturally acceptable techniques for managing the aggression (Steinert et al., 2010).

Different rates in prevalence of aggression depend on the countries in which the studies were conducted, methodology used, sample size and different periods of follow up (See Table 1.5: Prevalence of psychiatric aggressive episodes by country).

Table 1.5: Prevalence of psychiatric aggressive episodes by country

Country	**Methodology**	**Prevalence**	**Reference**	**Year**
USA	Review	10-13%	Davis	1991
Italian	Survey	3-7.5%	Biancosino et al., & Grassi	2009 & 2001
German	Survey	7.7%	Ketelsen, Zechert, Driessen, & Schulz	2007
Switzerland	Prospective	9.5%	Salamin, Schuwey-Hayoz, & Bickel	2010
Australia	Data collection from 11 units	12%	Carr et al.	2008
New Zealand	National survey	15%	Gale et al.	2002
Bahrain	Retrospective study	4.4%	Hamadeh, Alaiwat, & Ansari	2003

1.3 Aetiology of aggression in care settings

For the majority of aggressive/violent episodes in psychiatric care the people/patients have severe psychiatric disorders such as psychotic disorders (e.g. schizophrenia, schizoaffective disorder), affective disorders (e.g. bipolar disorder) or substance use disorder (e.g. use of alcohol, PCP, cocaine). Medical disorders that may produce psychiatric symptoms (tumours, thyroid gland disorders, etc.) and personality

disorders also account for some violent behaviour (Arseneault, Moffitt, Caspi, Taylor, & Silva, 2000; Brennan, Mednick, & Hodgins, 2000; Elbogen & Johnson, 2009).

Furthermore, violence in the psychiatric setting is not just limited to psychiatric and medical disorders; psychological and socio-demographic variables also increase the risk of committing an aggressive episode (Iozzino, Ferrari, Large, Nielssen, & de Girolamo, 2015). A systematic review and meta-analysis of empirical articles and reports of comparison studies of aggression and non-aggression within adult psychiatric in-patient settings found that several factors resulted in a higher risk of committing aggressive acts which include: being younger, male, involuntary admissions, not being married, history of previous admissions, violence and self-destructive behaviour (Dack, Ross, Papadopoulos, Stewart, & Bowers, 2013).

1.3.1 Common psychiatric disorders associated with aggression

Studies on aggression in psychiatric disorders conclude that people diagnosed with substance use disorder have the highest risk rate of being aggressive (Soyka, 2000; White, 1997). The probability of aggression increases if the individual with substance use disorder has a comorbid psychiatric

disorder (schizophrenia, bipolar, etc.). The list below is ordered – high to lower – for psychiatric disorders associated with violence.

a. Substance use

Substance use is a disorder categorised by the recurrent use of substances – alcohol and/or drugs - that can cause numerous problems such as social impairment, health complications, disability and a failure to meet responsibilities at work, educational settings or at home (American Psychiatric Association, 2013). The DSM categorises 'Substance use disorder' on evidence of impaired control, social problems, high-risk use and pharmacological criteria. Alcohol use in the world is placed in a range of 0-16%, while alcohol use *disorder* is ranged at 0-3% (World Health Organization, 2014).

i. Substance Use Disorder and aggression

Substance Use Disorder is a broad term and includes numerous types of drugs that affect various individuals differently. It is important to address these differences among the diverse types of drugs as each may influence violent behaviour differently (Miczek, DeBold, & van Erp, 1994). Again, below, the list is broadly in order of higher prevalence to lower – or less clear - rates of aggression/violence.

Overall, however, violence is more prevalent in terms of risk (if not managed) among people with substance use disorders than compared to the general population (Calogeras & Camp, 1975; Garrison, McKeown, Valois, & Vincent, 1993; White, 1997). This applies across the age ranges and genders. It is common for people diagnosed with impulse control disorders and pathological aggression to have comorbidity for substance use disorders (McElroy, Soutullo, Beckman, Taylor, & Keck, 1998).

ii. Alcohol and aggression

Alcohol is more strongly associated with violent aggression compared with other drugs such as heroin or marijuana (Heinz, Kluge, Schouler-Ocak, & Beck, 2016). Alcohol is the most commonly used drug from youth (Eaton et al., 2006) to the elderly (O'Connell, Chin, Cunningham, & Lawlor, 2003). It is the leading cause of numerous health problems, accidents and deaths worldwide (World Health Organization, 2014). In the USA it has been estimated that alcohol consumption (moderate and heavy) lead to 1200 homicides, 2067 motor vehicle accident deaths and 479 suicides among youths aged below 21 (in the year 2001 alone), (Swahn, Bossarte, & Sullivent, 2008). Numerous studies link alcohol consumption to a heightened risk of aggressive behaviour both in the community and in the emergency room setting (Cherpitel,

1993; Cherpitel, Pares, & Rodes, 1993; Foster, Vaughan, Foster, & Califano, 2003; White, 1997).

iii. Opiates and aggression

There are inconsistencies regarding the estimates of prevalence of aggression associated with opiates. Animal studies investigating the effects of opioids on aggression found that morphine and other opium compounds reduced aggression for a time (Espert, Navarro, Salvador, & Simon, 1993; Haney & Miczek, 1989) although that this effect may be reduced as tolerance develops (Rodriguez-Arias, Minarro, & Simon, 2001). However, there seems to be heightened risk of aggression in humans on morphine (Berman, Taylor, & Marged, 1993) codeine (Spiga, Cherek, Roache, & Cowan, 1990) and heroin (Hoaken & Stewart, 2003). Risk of aggression in heroin users, however, may be more related to personality traits rather than the drug effects (Gerra et al., 2001). In a Spanish study, in which files of 578 people arrested by the police were scrutinised, the heroin users were more likely *not* to be aggressive compared to people who were not users (Morentin, Callado, & Meana, 1998). Further animal studies noted how, although the casual use of opiates produces feelings of ecstasy and euphoria, chronic use may lead to behaviour and mood changes and how immediate cessation can cause heightened aggression (Hoaken &

Stewart, 2003). It is thought that opiate-linked aggression during *withdrawal* is particularly prevalent in people with certain predisposing personality traits (Tidey & Miczek, 1992, 1992).

iv. Psychostimulants and aggression

Psycho-stimulants have a reputation for being the class of drugs – other than alcohol - most associated with aggression (Taylor & Hulsizer, 1998). There are various reports from both community and hospital settings that cocaine is responsible for violent behaviours (Brody, 1990; Klee, 2001; Miczek & Tidey, 1989). The 'experimental' literature looking into cocaine administration in humans has yet to show a significant link between cocaine and increased violence. One study undertaken in a controlled setting showed that high doses of cocaine is associated with violent behaviour (Licata, Taylor, Berman, & Cranston, 1993). In the emergency setting, one study reviewed 311 consecutive psychiatric ER patients and reported that a negative relationship existed – patients who were tested positive for cocaine were *less* aggressive than people who did not test positive for cocaine (Dhossche, 1999). Another ER study found that aggression by people under the influence of cocaine was rare but aggression did occur if the person was severely intoxicated (Brody, 1990).

Pihl, Peterson, and Lau (1993) state the relationship between amphetamines and aggression is multifactorial. People who are prone to abuse amphetamines are more likely to manifest uninhibited displays of aggression. Psychopathy and antisocial personality disorder have been linked with high sensation seeking which, in turn, leads to greater chances of drug use – notably psychomotor stimulants. Secondly, intense psychological dependence on psycho-stimulants may make users who are in mild or severe withdrawal states more violent (Moeller et al., 1997). This research group concluded that, in inpatients newly admitted for treatment of cocaine use dependence, aggressive behaviour was predicted only by previous aggressive behaviour but not on cocaine craving, withdrawal symptoms, quantity of cocaine used or time length of last usage. Third, it is a possibility that aggression is a means to attain more drug since stimulants may be difficult to attain as well as expensive (Beaudoin, Hodgins, & Lavoie, 1993). Finally, psycho-stimulants can cause hallucinations and delusions – and since psychotic episodes are associated with violent behaviour (Coid et al., 2013; Large, Mullin, Gupta, Harris, & Nielssen, 2014), this may be part of the cause of why users of amphetamines may be violent.

b. Schizophrenia

Schizophrenia is a chronic brain disorder that has a life time prevalence of around 1% (Carr, Green, & Bell, 2017). It is categorised by symptoms of delusions, hallucinations, cognitive disturbances such as difficulty thinking and concentration, and lack of motivation (American Psychiatric Association, 2006).

i. Aetiology and prevalence

Schizophrenia affects both men and women equally though the onset is earlier in males (Eranti, MacCabe, Bundy, & Murray, 2013). The rates are similar in all ethnic groups (Eranti et al., 2013). Schizophrenia may be a group of disorders where causes and symptoms vary between individuals (Bentall, 2013). The causes of schizophrenia are unknown but it is well-established that both genetic and environmental factors equally play a role (Miller, 2016). Behavioural management and use of psycho-pharmacology such as antipsychotics can greatly reduce the symptoms (Bruijnzeel, Suryadevara, & Tandon, 2014).

In the USA approximately 4.3 million ER psychiatric emergency visits occur annually (approaching 5.4% of all ER visits). Psychotic disorders, including schizophrenia, make up around 21% of those ER visits – 900,000 visits annually.

Schizophrenia is disproportionately common among homeless people, with an incidence of 27% (D'Amore, Hung, Chiang, & Goldfrank, 2001).

ii. Schizophrenia and aggression

Schizophrenia is associated with a higher risk of violence compared to the general population if not managed accordingly. However, several studies including reviews and meta-analyses examined the relationship between schizophrenia and violence and the comorbid risk factors that contributed to a higher risk of violent behaviour (See Table 1.6: Schizophrenia and aggression) (Wehring & Carpenter, 2011). Cohort studies of violent aggressive behaviour in schizophrenia showed that, if not managed accordingly, nearly fourfold of those diagnosed with schizophrenia were at a higher risk to participate in violent and aggressive behaviour compared to people with no history of psychiatric disorder (Angermeyer, 2000). Variables that seem to act as major risk factors for violent behaviours in this group were younger age, higher rehospitalisation rate, comorbid personality disorders mainly antisocial personality disorder and a history of involvement in crime (Bonta, Law, & Hanson, 1998). Others have found risk factors to be substance use, psychotic symptoms such as hallucinations, bizarre behaviours, delusions, organic neurological disorders, being male, and of

low socio economic status, unskilled, uneducated and unmarried (American Psychiatric Association, 2006).

Table 1.6: Schizophrenia and aggression

Ref	Methods	Outcome	Main conclusion
Bonta et al. (1998)	Meta-analysis on factors predicting criminal recidivism, comparing mentally disordered, including schizophrenia and non-disordered offenders	Criminal History variables were the best predictors (r= -4.2)	Same variables predict criminal recidivism in both mentally disordered and non-disordered populations
Douglas, Guy, and Hart (2009)	A meta-analysis on the contribution of psychosis on violence	All effect sizes: (k=885) (M=3.50) (95% CI: 2.53 to 4.46)	Moderating factors more essential as predictors of violence than psychosis
Fazel, Gulati, Linsell, Geddes, and Grann (2009)	A systematic review and meta-analysis on studies investigating the relation between schizophrenia and violence, including homicide	In men, ORs for the comparison of violence in those with schizophrenia and other psychoses with those without mental disorders varied from 1 to 7 with substantial heterogeneity (I2 = 86%). In women, ORs ranged from 4 to 29 with substantial heterogeneity (I2 = 85%).	Schizophrenia predicts violent offending, but the excess risk is mediated by substance abuse comorbidity
Hodgins (2008)	A review article on schizophrenia, aggression and treatment implications	See review.	Schizophrenia contributes to violence, but in patients with a history of early violent behaviour, psychotic symptoms has little influence
Modestin (1998)	An overview of the relation between mental disorders, schizophrenia and violence	All crimes: 95% CI: 0.7-1.3	Schizophrenia contributes to violence, and is enhanced with comorbid psychoactive substances
Nielssen and Large (2008)	Rate of homicide during first episode psychosis and after treatment.	Meta-analysis of these studies showed that 38.5% (95% confidence interval [CI] = 31.1%–46.5%) of homicides occurred during the first episode of psychosis, prior to initial treatment.	Rate of homicide is disproportionately high compared to after treatment in schizophrenia. First-episode psychosis is a major risk factor for violence.
Taylor (2008)	A review on the relation between psychosis and violence with specific focus on schizophrenia	Review concludes there is a significant relationship between violence while having a psychotic episode.	Schizophrenia contributes to violence in groups of patients with no criminal behaviour before illness onset, but not in groups with prior delinquency
Walsh, Buchanan, and Fahy (2002)	A review on violence and schizophrenia	Review concludes there is a significant relationship between violence and schizophrenia.	The association between schizophrenia and violence is confirmed, but mediated by substance misuse
Volavka and Citrome (2008)	A review of the relation between schizophrenia and the heterogeneity of violence, including moderating factors such as personality disorder	Review concludes the rates of violence is increased with schizophrenia and personality disorders.	Schizophrenia contributes to violence in groups of patients were no history of violence is found

iii. Schizophrenia and substance use

The risk of violence in schizophrenia increases if disorders such as substance use disorders coexist (Short, Thomas, Mullen, & Ogloff, 2013). For example, a study analysing the prevalence of homicide in schizophrenia found that 6% of homicides match with the diagnosis of schizophrenia and the risk of homicide is increased 8-fold in people with schizophrenia and comorbid substance use disorder – mainly alcohol use (Richard-Devantoy et al., 2013). Approximately 50% of people with schizophrenia will fulfil the dual diagnosis of schizophrenia and substance use at some point during their lifetime (Regier, Farmer, Rae, & et al., 1990). Though tobacco and caffeine are the most common substances of abuse, alcohol, cannabis and cocaine are strongly associated with people who have a dual diagnosis of schizophrenia and substance use disorders (Schneier & Siris, 1987). People with schizophrenia and comorbid substance use are mainly men, have a younger illness onset, higher prevalence of depressive symptoms, fewer negative symptoms, lower treatment compliance and a higher incidence of violent behaviour (Addington & Addington, 1997; Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006; Janssen et al., 2006; Mueser, Drake, & Wallach, 1998; Talamo et al., 2006). In conclusion, a review done by Rund (2018) looking at the association between

schizophrenia and violence reported in its summary of findings that substance use is the most robust evidence of all single factors linking schizophrenia to a higher risk of violence.

c. Bipolar Disorder

Bipolar Disorder is a mood disorder categorised with periods of depression and elevated mood. Depending on its severity, the milder form of this elevated mood is known as hypomania while mania is severe and even life-threatening in itself (American Psychiatric Association, 2006). In states of mania, psychotic symptoms such as hallucinations and delusions can occur. During hypomania, a person can experience elevated mood, energy or irritability. People have poor sleep patterns during hypomanic and manic episodes that can last days to weeks. Decisions may be ill judged with little or no regard for consequences. During depression, people with bipolar disorder may have a very poor outlook on life, difficulty concentrating, with low mood and energy.

i. Prevalence

Bipolar disorder is listed as the 6th leading disability worldwide and has had lifetime prevalence rates estimated to be up to 3% in the general population (Schmitt, Malchow, Hasan, & Falkai, 2014). The WHO found that prevalence and incidence of Bipolar Disorder was very similar across the world at around

0-5% lifetime prevalence (World Health Organization, 2002). It affects men and women equally. However, severity differs widely across the globe due to certain variables such as disability adjusted life year rates that tend to be higher in low/middle income countries as people there may have less access to medication (Ayuso, Sala, Luis, & Carbo, 2003). The risk of suicide among people with bipolar disorder is higher than the general population (>6% in a range period of 20 years), while harming oneself will occur at least once during their lifetime in 60% of people (Volavka, 2014). Bipolar disorder is also highly associated with comorbid disorders such as substance use and anxiety (Judd & Akiskal, 2003).

ii. Bipolar Disorder and aggression

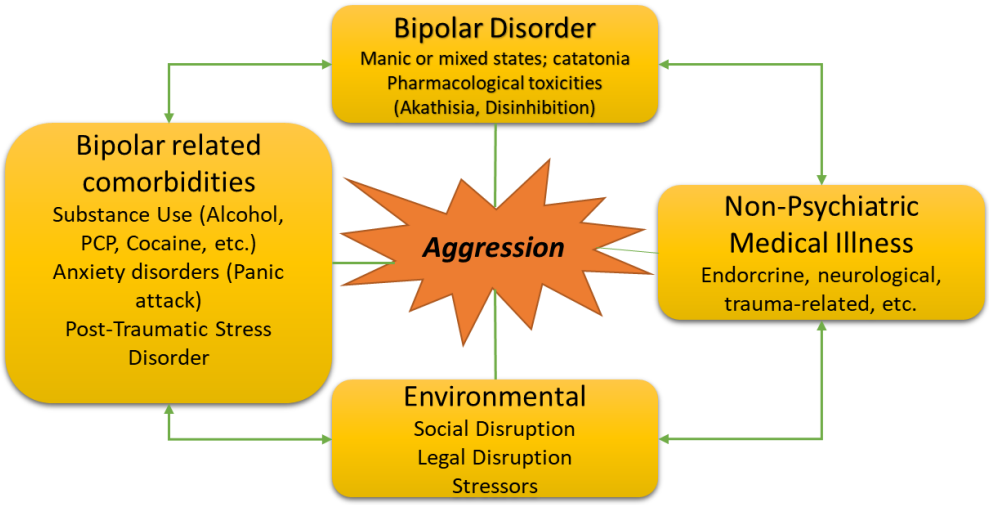
There are several factors that explain the context of violent aggression in mania. A cross sectional study assessed 237 manic patients for 20 symptoms. The factor analysis showed that violence was associated with paranoid ideation and irritability (Cassidy, Forest, Murry, & Carroll, 1998).

The link between bipolar disorder and violence tends to be strongest during acute phases of the illness. In the USA, manic patients showed aggressive behaviour in the community two weeks prior before being hospitalised as well as showing higher rates of violent behaviour during the first three days of

being hospitalised (Feldmann, 2001; McNiel, Binder, & Greenfield, 1988). A USA national survey (sample size 43,094 adults) investigated the lifetime prevalence of violent behaviour and the lifetime prevalence of psychiatric disorders (Pulay et al., 2008). The results showed the lifetime prevalence of violent behaviour after 15 years of age was 0.66% in people without any psychiatric disorder but rose to 25% and 14% in Bipolar I (Disorder has episodes of full blown mania and depression) and Bipolar II (Disorder has hypomanic episodes rather than full blown mania but still retains depression episodes) (American Psychiatric Association, 2013). Bipolarity is said not to be goal-oriented, therefore targets of aggressive behaviour may be random (Tardiff, 1984). People with bipolar illness at risk of aggressive behaviour may become highly aggressive in the emergency setting when they feel restricted or when staff members in the hospital place rules on them or have mismanaged the condition. The probability of violence is increased during manic episodes of people with bipolar disorder compared with episodes of depression. (Yesavage, 1983). Risk factors that increase chances of violent behaviour in bipolar disorder are conceptual disorganisation, auditory hallucinations, odd thought content, paranoid ideation, uncooperativeness and irritability (Pliszka, 2000). According to Swann (2007), the risk of aggression in

people with bipolar disorder is caused by a multitude of factors (See Figure 1.1) and the addition of each variable increases the likelihood of aggressive incidents.

Figure 1.1: Bipolar and aggression



iii. Bipolar and co-morbidity

Fan and Hassell (2008) reviewed 32 studies reporting on the prevalence and effect of comorbid personality disorders or abnormal personality traits in bipolar disorder patients. Their results showed that bipolar patients had a significantly higher prevalence rate of having a personality disorder than the general population. The paragraph below will examine the effects of bipolar disorder and personality disorder as comorbidity.

A cross sectional study investigated 576 manic/hypomanic patients with a detailed instrument assessing symptoms including aggression, irritability, uncooperativeness, lack of

patience and lack of insight. The cluster analysis suggested the existence of four subtypes of mania, one of which was labelled as 'aggressive' (Sato, Bottlender, Kleindienst, & Moller, 2002).

In a study that examined suicide as a comorbidity in bipolar disorder, 21 people with a history of suicide attempts were compared with a matched set of people without a history of attempting ending their own life (n=23). The results showed that bipolar patients who attempted suicide had significantly greater scores on scales measuring violence and lifetime history of aggression (Oquendo et al., 2000). In a similar study examining bipolar patients, suicide attempters (n=27) and comparing this group with bipolar patients, non-attempters (n=25), the 'attempters' had higher levels of impulsiveness and hostility (Michaelis et al., 2004). Another study that assessed one hundred DSM-IV diagnosed Bipolar I patients (N=73) and Bipolar II (N=27) and the results showed that 30% of patients met DSM-IV criteria for a cluster B personality disorder (17% borderline, 6% antisocial, 5% histrionic, 8% narcissistic). Cluster B diagnoses were significantly linked with histories of childhood emotional abuse ($p = .009$), physical abuse ($p = .014$), and emotional neglect ($p = .022$), but not on sexual abuse or physical neglect. Cluster B comorbidity was associated with significantly more

lifetime suicide attempts and current depression. Lifetime suicide attempts were significantly associated with cluster B comorbidity (OR = 3.195, 95% CI = 1.124 to 9.088), controlling for current depression severity, lifetime substance abuse, and past sexual or emotional abuse (Michaelis et al., 2004).

There are several factors that explain the context of aggression in mania. Initial data on 983 people from the Systematic Treatment Enhancement Program for Bipolar Disorder showed comorbidity rates associated with age of onset of mood symptoms. Alcohol abuse comorbidity was in the range of 32-46% and other drug abuse 15-34% - all depending on age of onset. Early onset was associated with higher rates of comorbidity (Perlis et al., 2004). In a study where the impact of alcohol use on symptom presentation was investigated in patients with (*n*=60) and without acute bipolar mania (*n*=196) current alcohol abuse, the comorbid group showed higher levels of impulsivity and violent behaviour (Salloum, Cornelius, Mezzich, & Kirisci, 2002).

Bipolar disorder with antisocial personality disorder as a comorbid problem shows elevated risks of violent behaviour (Volavka, 2014). In a study of just over 43,000 adults representing the US population, examining the lifetime prevalence of aggressive behaviour and DSM-IV psychiatric

disorders, the prevalence of violent behaviour after age 15 years was 0.66% in persons without lifetime mental disorder (Latalova, 2009). This rose to 25% (Odds Ratio 3.72 95% CI 2.94–4.70) for bipolar I and 14% for bipolar II (OR 1.77 95% CI 1.26–2.49). These numbers represent a mixture of 'pure' bipolar disorders (without comorbid diagnoses) plus bipolar disorders with comorbid diagnoses (Latalova, 2009). Comorbidity of bipolar disorder with antisocial personality disorder showed higher levels of impulsivity and aggressive behaviour in this large sample (Grant et al., 2005).

Furthermore, Cluster B personality disorders and bipolar disorder overlap clinically and share impulsivity as a core feature (Henry et al., 2001). Having a personality disorder as a comorbidity has then shown to increase impulsivity – risk taking and violent backlash compared to patients without a diagnosis of a personality disorder (Dunayevich et al., 2000).

d. Personality Disorder

Personality is defined as a set of behavioural and psychological traits that differentiate between human individuals (American Psychiatric Association, 2013). Personality Disorders (PD) are a group of mental disorders characterised by maladaptive signs of behaviour, cognition, inner experiences conveyed across multiple context and deviating strongly from the

individual's cultural norm (American Psychiatric Association, 2013). Personality disorders are diagnosed in 40-60 percent of psychiatric patients making PD the most prevalent of psychiatric diagnosis (American Psychiatric Association, 2013).

i. Prevalence

The average rate of PD in the community - based on findings of six major studies undertaken in 2008 - was estimated at approaching 11% (Lenzenweger, 2008). Specific personality disorders range from 2-3% in the general population. The common varieties include antisocial, borderline, histrionic and schizotypal. The less common such as narcissistic and avoidant range from 0.5 to 1% (Kaplan, 2005). In the USA, combining screening data from the national comorbidity survey between 2001 and 2003 with interviews from respondents found a prevalence of 9% of personality disorders (Lenzenweger, 2006). In the UK, a national epidemiological study on personality disorders using the DSM-IV screening criteria reclassified categories into levels of severity rather than solely diagnosis (Yang, Coid, & Tyrer, 2010). They found the majority of people show *traits* of a personality disorder but not a full-blown diagnosis. The number of the severe cases was 1.3%. Finally, a global survey across 13 countries by the WHO, also using DSM-IV screening criteria, reported a prevalence estimate of around 6% (Huang et al., 2009). This

survey noted the rate varied depending on variables such as demographic and socio-economic factors, while functional impairment was increased by comorbid mental disorders (Huang et al., 2009).

ii. Personality Disorders and aggression

Symptoms of narcissistic, paranoid or passive aggressive personality disorder may have higher risk of committing violent acts compared to controls (Johnson et al., 2000). In the same study, paranoid personality disorder was associated strongly with risk of initiating physical fights while narcissistic personality disorder was more associated with environmental destruction such as vandalism or arson and threatening to injure others physically. Passive aggressive personality disorder was also associated with threatening to initiate physical fights and participate in arson or vandalism (Johnson, Smailes, Cohen, Brown, & Bernstein, 2000). A community longitudinal prospective study investigated whether personality disorders during adolescence were associated with higher risk for aggressive behaviour during adolescence and early childhood. The samples were 717 youths from New York and they and their mothers were interviewed in 1983, 1985-1986 and 1991 to 1993. The results, according to the DSM-IV, showed that Cluster A and Cluster B personality disorders were more likely to commit violence (Johnson et al., 2000).

Another study investigating the risk of crime assessed a sample of 456 male inmates of prisons situated in Quebec with the DIS (Diagnostic Interview Schedule); 107 received a diagnosis of a major disorder and 71 an additional diagnosis of antisocial personality disorder. The results showed that those with APD had a significant childhood history of criminal activity and antisocial behaviour, endorsing, on average, eight of ten possible indices. In comparison, the mentally disordered inmates without APD endorsed on average two indices (Hodgins & Gaston, 1989).

1.4 Management of aggression in psychiatry

There may well always be aggression in the psychiatric emergency because of a combination of factors inherent to the patient/client, such as personality, physical symptoms or intense mental distress; and extrinsic variables such as attitude and behaviours shown by staff and other people as well as the physical environment and restrictions that inhibit the patients' movements (Harwood, 2017). Accepting this, appropriate measures should be taken to best ensure prevention, de-escalation and, as the last resort when all else has failed, eventual management of aggressive behaviour for the safety of all involved. This thesis focuses on the situation when all else has failed but it cannot be emphasised enough that rapid tranquilisation takes place only after a series of failures and, assuredly, prevention is assuredly better than any 'cure'.

1.4.1 Prevention

An aggressive episode does come with warning signs and if taken into consideration by professionals, preventing the episode from escalating can minimise the number of emergency episodes that occur (Ketelsen et al., 2007). The professionals at work may take note of signs that could serve as indicators of aggression (Amore et al., 2008).

1.4.2 De-escalation measures

If the clinical situation becomes difficult and has escalated into a potential threat (patient becomes physically or verbally aggressive), de-escalation measures need to be used. De-escalation can be understood as the process of de-fusing, negotiation and conflict resolution. It is sometimes referred to as the 'non-pharmacological' or 'behavioural' strategies which means de-escalation is limited to non-restrictive measures – no use of tranquilising using pharmacology or physical restraint or seclusion (Cowin et al., 2003).

Price and Baker (2012) synthesised 11 papers on de-escalation techniques, identified common themes associated with de-escalation measures in the current context. Such measures consistently involve a complex interplay of several factors involving staff, timing, the environment and the strategy or technique employed.

a. Staff

i. Training

In the UK NICE guides that health and social care organisations should provide de-escalation training techniques to staff that enables them to:

- Recognise the early signs of agitation, irritation, anger and aggression

- Understand the likely causes of aggression or violence, both generally and for each service user
- Use techniques for distraction and calming, and ways to encourage relaxation
- Recognise the importance of personal space
- Respond to a service user's anger in an appropriate, measured and reasonable way and avoid provocation (National Institute of Clinical Excellence, 2015).

ii. Characteristics

Effective de-escalators have genuine concern for the patient and are open, non-judgemental, honest and supportive (Carlsson, Dahlberg, & Drew, 2000). These traits provide better opportunities for building trust between the de-escalator and the patient which, in turn, assists in making appeals for self-control more likely to be accepted (Duperouzel, 2008). Being empathetic is also important as it makes the patient feel understand and validates their experiences which reduces the risk of having an aggressive reaction (Duperouzel, 2008).

iii. Ability to maintain personal control

Effective de-escalators remain calm even though they may be experiencing anxiety internally (Duperouzel, 2008). Staff showing a state of calm is believed to help the patient manage their feelings of aggression by communicating to them that despite their frustrations, they are trusted not to be violent (Lowe, Wellman, & Taylor, 2003).

iv. Verbal and non-verbal skills

Verbal techniques include using a calm and gentle tone of speech when addressing the patient and language should be tactful. Non-verbal techniques include body language where staff should be attentive of their posture, eye contact, proximity, touch and facial cues. Active listening should be utilised so the patient knows he/she is being listened to and cared for (Ryan & Bowers, 2005).

v. Ability to engage with the patient

Staff should seek to create a bond with the aggressive patient who would establish a sense of mutual regard that would diminish the need for the patient to be aggressive (Carlsson et al., 2000; Duperouzel, 2008). With the focus on promoting the autonomy of the patient using minimum restrictions as possible, it demonstrates the staff's trust of the patient which confirms their dignity and humanity that ultimately helps to

create a sense of equality between both staff and patient (Delaney & Johnson, 2006).

b. Timing - when to intervene

The bulk of the literature states that early intervention is vital to successful de-escalation but there was also an acknowledgement that unnecessary interventions could intensify problems (Johnson & Delaney, 2007; Lowe et al., 2003). The decision on whether or not staff should intervene are based on:

- Knowledge of the patient
- Whether the patient's behaviour deviates from their normal presentation
- Degree of danger associated with their behaviour
- Their potential impact on others

c. Environment - safe conditions

It is imperative to have an overview and an assessment as to what level of staff support is required to safely de-escalate the patient while bearing in mind that physical force can escalate rather than de-escalate the aggressive patient in question (Delaney & Johnson, 2006; Duperouzel, 2008). Environmental assessments should also be considered as potential weapons and other hazardous materials could be present (Duperouzel, 2008). Exits for staff to vacate the area as safely as possible

should be noted (Duperouzel, 2008). The patient should also be motivated and encouraged to move to a safe and quiet area of the ward that is separated from other patients and uninvolved staff. This should be done without obvious intention otherwise the patient might be aggravated further (MacKay, Paterson, & Cassells, 2005).

d. Strategies for de-escalation

There are multiple methods for de-escalation as noted above and deciding the best strategy is, currently, out of necessity, an instinctive, intuitive process that requires creativity and is based on the individual needs of each patient displaying an aggressive episode (Carlsson et al., 2000). Using methods mentioned above i.e. being empathetic, verbal and non-verbal cues are useful in assessing the patient's emotional state which would assist in the formulation of appropriate interventions (Carlsson et al., 2000; Delaney & Johnson, 2006; Duperouzel, 2008). It is important that staff interventions are proportionate to the risk being posted by the aggressive patient (MacKay et al., 2005). What is missing from the literature in this area are tested techniques in randomised trials. This leaves this whole area of care open to well-intended expensive investment which could not be as effective as had been hoped.

1.4.3 Active management

If a violent incident is imminent after de-escalation techniques have failed, someone (often doctors) will need to intervene. The criteria to act is if the patient poses a risk to seriously harm oneself, other patients, visitors or members of staff (Duxbury & Whittington, 2005). Destruction of property or the care environment is another indicator. These are all calls on the judgement of the attending physician – a responsibility that can be shared with other medical or nursing colleagues. The aim of the attending physician is to take the necessary action to end the incident, ensure the safety of all and to minimise physical and psychological harm to the aggressive patient (George & Carson, 2000).

a. Coercion

Box 1.2: Definition of coercion

> Definition
>
> Coercion - any action or threat of actions which compels the patient to behave in a manner inconsistent with his own wishes (Edwards, 1982).

Often, these measures are implemented through the use of coercion.

The concept of coercion exists on a continuum, which means it can be direct - such as the use of restraint (physical holding or through mechanical devices) or seclusion (where a door is

locked and patient is kept in a holding) or as a pharmacological intervention whereby medication is given in the absence of consent. Coercion can also be subtle whereby staff can be intimidating - usually by presence (i.e. large groups in close proximity to patient) or forceful suggestion-like threats if medication is not taken orally more implicit forms of managements will be used (Bowers, Van Der Merwe, Paterson, & Stewart, 2012).

i. Restraint

Coercive active management may involve physical restraint/s and/or rapid tranquilisation with drugs (Keski-Valkama, 2010). Physical restraint is employed to ensure the patient does not harm self or others while rapid tranquilisation is given within the aim of sedating the aggressive patient to a state of calm or tranquillity – or sleep. (Distasio, 1994; George & Carson, 2000). There is clearly variation in which approaches are used at any one place and time. For example, Figure 1.2: How physical restraint practice differs by region (Migon et al., 2008) illustrates how use of physical *restraints* may be routine in some places and never used in others. For example, restraints are assiduously avoided in the UK, but are routine in many places such as the USA and the Scandinavian countries. The avoidance of restraints may have led to a UK tradition of employment of greater doses of medication to 'hold' a person

than other countries (Pilowsky, Ring, Shine, Battersby, & Lader, 1992). This tradition may have been offset by much more clear UK guidance (National Institute of Clinical Excellence, 2015) and monitoring (POMH-UK, 2017). However, the need for restraining - whether by use of restraints or staff - and the use of rapid tranquilisation - seems ubiquitous (Migon et al., 2008).

ii. Rapid tranquillisation

Box 1.3: Definition of rapid tranquilisation

Definition

For the purpose of this thesis, rapid tranquillisation (RT) is defined as a 'chemical restraint' whereby the use of pharmacological medications is given to control a person's behaviour – usually with the target of having the patient become calm, tranquil or asleep.

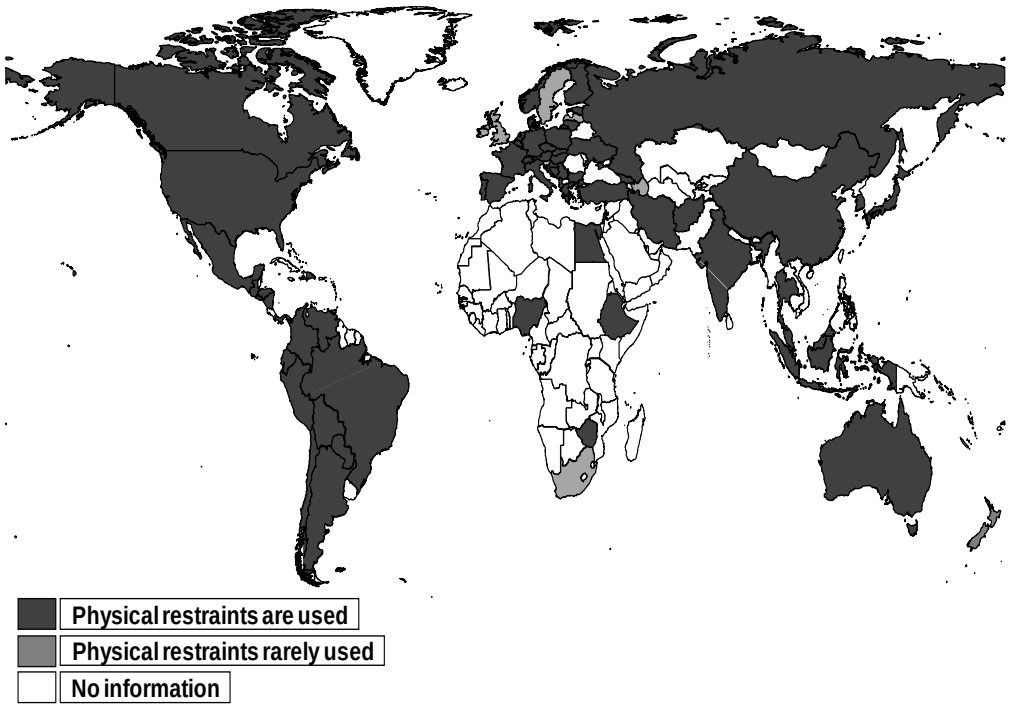
Rapid tranquillisation (RT) is not a 'treatment' for a persons' mental health condition but, rather, a short-term management technique for severely agitated and/or aggressive behaviour in people experiencing psychotic distress. Due to its restrictive nature, RT should only be used as last resort when all other attempts to calm a situation via prevention (being environmentally aware and ensuring that adequate numbers of

staff are present on ward) and de-escalation (talking to and verbally trying to calm the person) have failed. These interventions should always be used in a way that respects human rights and should never be used to manage patients as a substitute for adequate staffing (Department of Health, 2015).

iii. Seclusion and restraint

Seclusion and restraint are interventions currently permitted for use in mental health services and other settings to control or manage a person's behaviour (Brophy, Roper, Hamilton, Tellez, & McSherry, 2016). Seclusion technically refers to the deliberate confinement of an aggressive individual to a room or area that he or she is restricted from moving freely (even an expansive but enclosed compound), and restraint encompasses the use of bodily force (physical restraint) or a device (mechanical restraint/s) (Brophy et al., 2016).

Figure 1.2: How physical restraint practice differs by region (Migon et al., 2008)



1.5 Policy and practice

1.5.1 Evolution

Society's attitude towards - and tolerance of - behaviour thought due to mental illnesses is the function of a complex interplay of culture, religion, education, experience and setting. The collective attitude also changes across time - both progressively and in stepwise fashion. For example, the progression resulting from the pioneering humanitarian reforms of one leading thinker - Phillippe Pinel in the early 19th century (Pinel, 1806)– and then again William Tuke here in the

UK (Tuke, 1813) – probably emerged from the collective changing attitudes of the time. The establishment of the mental asylums in the UK, triggered as a reaction to the epidemic of neuro-syphilis of those returning from the Napoleonic wars, evolved into an enormous humanitarian investment in Victorian England for the demented, deluded and delirious (Scull, 1993).

The progress and stepwise evolution can, however, also run in reverse. For example, in the UK, as the ill-considered laws of the late 19th century took hold, overcrowding and institutional attitudes set in and abuses of power and treatment were rife (Takabayashi, 2017). Although wonderful examples of humane use of asylums remain (Rivers, 1919; Tiffany, 1891), reference here too the day of these institutions were numbered. However, the slow attitudinal changes [and the running sore of the scandals of the early 20th century] only came to a fuller fruition in the era of medication (Scull, 1993) and, in this country, the establishment of the NHS.

Attitudes to the management of violence thought due to mental illness or impairment have also evolved – although it could be argued - lagged some way behind society's other approaches to mental problems. Painful stepwise evolution has taken place. The scandals of lingering institutional abuses (Hill, 2012; The Care Watchdog, 2019) paired with clinical and

academic push (Paterson, McIntosh, Wilkinson, McComish, & Smith, 2013) as well as public outrage ("Inquest family calls for restraint methods inquiry", 2011; The Care Watchdog, 2019) albeit that the latter is fickle (McNaughton, 2015). A report give impetus towards more regulated management of aggression and violence thought due to mental disorder (McNaughton, 2015). Back in 1992, Lynn Pilowsky undertook a pioneering survey in what was an un-named "large South London hospital" of drug treatments used in rapid tranquilisation (Pilowsky et al., 1992). She did this, in part, to highlight the chaos of treatment in this area in the UK. Professor Clive Eliot Adams stated, upon meeting Joseph Dib (myself) for the first time in September 2016, that Doctor Pilowsky was pleased her work triggered other surveys of practice in different countries (Adams, 2016). Certainly, the survey undertaken in the Instituto Philippe Pinel (Rio de Janeiro) was triggered by surprise at what one Brazilian thought to be the inhumane treatments given in the UK (Huf et al., 2002) and so paved the way for the first TREC randomised trials (TREC Collaborative Group, 2003). National and international guidance and policy also evolves across time. For example, in the UK the Royal College of Psychiatrists, acutely conscious of criticism and stigma triggered by, amongst other things, iatrogenic scandal made enormous

efforts to generate relevant guidance (Royal College of Psychiatrists, 1993), (Royal College of Psychiatrists, 1995), (Royal College of Psychiatrists, 1996), (Royal College of Psychiatrists, 1998).

Although these early attempts did come in for criticism (Palmer, 1996) the concurrent evolution of clinical epidemiology (Sackett, 1985), the NHS's pioneering adoption of industrialisation of the systematic reviewing of trials (Cochrane Collaboration, 1993) and the establishment of York's NHS Centre for Reviews and Dissemination with its bulletins on effective health care (The Centre for Reviews and Dissemination, 1994) all paved the way for the NHS's National Institute of Clinical Excellence (NICE) and their guidance. There are now many versions of national guidance (Department of Health: Government of Western Australia, 2006; Occupational Safety and Health Administration, 2017; Queensland Health, 2008) but NICE's output does represent an imperfect but genuine example of a highly evolved state-of-the-art guidance used to under-pin national policy.

a. NICE guidelines

The NICE guidance attempted to tread a near impossible balance between well-apprised best evidence and local clinical and lay consensus. This was in the wise recognition that even

the highest-grade evidence is of lessened value without a local will to adopt and, conversely, widely used local practice, however well intentioned, is undermined by lack of highest-grade evidence. Such guidelines also involve in the light of valid criticism, new research and attitude change. Since the publication of the first NICE guidelines relevant to management of violence in adults with mental health difficulties (National Institute of Clinical Excellence, 2005) there have been many more expressions of concern regarding this area of care (Brophy, Roper, Hamilton, Tellez, & McSherry, 2016). The more recent version of the guidance (National Institute of Clinical Excellence, 2015) is a sophisticated document trying to tackle the [perhaps impossible] complexities of this area of care. The authors of the new NICE guidance, clearly conscious of the UK's Department of Health push for positive and proactive care reducing the need for coercive treatments (Department of Health, 2014) emphasise how every effort is needed to avoid use of coercive treatments such as rapid tranquilisation. The development of what seem better techniques of avoidance of coercive treatments (Duxbury et al., 2019) along with the recognition of the harm such treatments can cause (Cusack, Cusack, McAndrew, McKeown, & Duxbury, 2018), serves, hopefully, to make rapid tranquilisation, ever-more an

approach of last resort. The push away from coercive techniques, however, is hampered by the limited high-grade evidence available for the effects of the prevention or de-escalation techniques. Nor does this humanitarian push in any way offset the need for generation of best evidence of the different treatments used for rapid tranquilisation. The technology appraisal of the NICE guidance highlights the limited evidence in all aspects of this area of care (National Institute of Clinical Excellence, 2015). This guidance, despite having been tailored for use in the UK's NHS, has, nevertheless, been adopted by other nations (Ranjan & Chandra, 2005).

According to the NICE guidelines of violence and aggression [NG10], observation and de-escalation techniques should precede rapid tranquilisation (National Institute of Clinical Excellence, 2015)

Table 1.7: Levels of observation according to NICE recommendations (National Institute of Excellence, 2015)

Observation	
Levels of observation	
Low-level intermittent observation	Baseline level of observation in a specified psychiatric setting. The frequency of observation is once every 30–60 minutes.
High-level intermittent observation	Usually used if a service user is at risk of becoming violent or aggressive but does not represent an immediate risk. The frequency of observation is once every 15–30 minutes.
Continuous observation	Usually used when a service user presents an immediate threat and needs to be kept within eyesight or at arm's length of a designated one-to-one nurse, with immediate access to other members of staff if needed
Multi-professional continuous observation	Usually used when a service user is at the highest risk of harming themselves or others and needs to be kept within eyesight of 2 or 3 staff members and at arm's length of at least 1 staff member.

Table 1.8: Manual and Mechanical restraints as recommended by NICE (National Institute of Clinical Excellence, 2015)

De-escalation techniques
Manual restraint
• Health and social care provider organisations should ensure that manual restraint is undertaken by staff who work closely together as a team, understand each other's roles and have a clearly defined lead. • When using manual restraint, avoid taking the service user to the floor, but if this becomes necessary: - Use the supine (face up) position if possible or, - If the prone (face down) position is necessary, use it for as short a time as possible. • Do not use manual restraint in a way that interferes with the service user's airway, breathing or circulation, for example by applying pressure to the rib cage, neck or abdomen, or obstructing the mouth or nose. • Do not use manual restraint in a way that interferes with the service user's ability to communicate, for example by obstructing the eyes, ears or mouth. • Undertake manual restraint with extra care if the service user is physically unwell, disabled, pregnant or obese. • Aim to preserve the service user's dignity and safety as far as possible during manual restraint. • Do not routinely use manual restraint for more than 10 minutes. • Consider rapid tranquillisation or seclusion as alternatives to prolonged manual restraint (longer than 10 minutes). • Ensure that the level of force applied during manual restraint is justifiable, appropriate, reasonable, proportionate to the situation and applied for the shortest time possible. • One staff member should lead throughout the use of manual restraint. This person should ensure that other staff members are: - Able to protect and support the service user's head and neck, if needed - Able to check that the service user's airway and breathing are not compromised - Able to monitor vital signs - Supported throughout the process. • Monitor the service user's physical and psychological health for as long as clinically necessary after using manual restraint.
Mechanical restraint
• Health and social care provider organisations should ensure that mechanical restraint in adults is used only in high-secure settings (except when transferring service users between medium- and high-secure settings as in recommendation 1.4.36) and its use is reported to the trust board. • Use mechanical restraint only as a last resort and for the purpose of: - Managing extreme violence directed at other people or - Limiting self-injurious behaviour of extremely high frequency or intensity. • Consider mechanical restraint, such as handcuffs, when transferring service users who are at high risk of violence and aggression between medium- and high-secure settings. In this context, restraint should be clearly planned as part of overall risk management.

Table 1.9: NICE recommendations for rapid tranquilisation (National Institute of Clinical Excellence, 2015)

Injection route	Drugs included
IM Monotherapy	Lorazepam
IM Combinations	Haloperidol plus promethazine

1.5.2 Policy regarding rapid tranquilisation

a. Transnational

There is no international consensus on the most effective treatment; guidelines are statements of consensus and they differ on which drugs to use (Nadkarni, Jayaram, Nadkarni, Rattehalli, & Adams, 2015). According to the Institute of Medicine (1990), clinical practice guidelines are defined as 'systematically developed statements of recommendation for patient management to assist practitioner and patient decisions about appropriate healthcare for specific situations.'

b. National

Cultural differences indicate that across countries, some forms of restrictive measures are more acceptable than others. The most stark example is the use of mechanical restraints which are prevalent in American, Australian, Canadian, majority of European countries and Lebanon (Guzman-Parra et al., 2016) but rarely permitted in the acute settings of the UK (National Institute of Clinical Excellence, 2015).

i. UK

UK's policies are based on liberal, Judeo-Christian principles, in a well-funded socialist health care system of a mature Western democracy. They are linked to - but not dictated by - best evidence. Every effort has been made to make them humanitarian, patient-centred, yet considerate of the needs of society. This, of course, makes them deeply flawed. The very liberality of the care culture to which they are applied – and the great strength of that – is also a weakness – allowing for variation in practice the extremes of which lead to dramatic malpractice (Hill, 2012). Laudable efforts to link guidance to evidence, and policy to that guidance, is another Achilles heel. Evidence is often weak or non-existent – again making all in this difficult area of care vulnerable to undertaking treatments of very limited worth.

NICE guidance – state-of-the-art though it is – and its link to policy does not yet avoid the trauma of these individual and collective incidents (Bonner, Lowe, Rawcliffe, & Wellman, 2002; Sweeney, Clement, Filson, & Kennedy, 2016). Despite this state of high evolution of guidance and policy, NHS practitioners continue to have a difficult time balancing patient safety and patients' rights (Beattie, Griffiths, Innes, & Morphet, 2019; Duxbury & Whittington, 2005).

ii. Lebanon

Currently, Lebanon has neither a national mental health policy nor a truly active mental health programme – at least partly due to multiple barriers in the mental healthcare setting (Chahine & Chemali, 2009).

Table 1.10: Barriers to the delivery of mental health in the primary care setting in Lebanon (Chahine & Chemali, 2009)

Government-related factors
• Absence of mental health care on the MoPH agenda.
• No sharing of a common vision among MoPH, WHO and mental health professionals.
• What WHO has "on paper" is different from what is happening "on the ground".
• Conflicts of interest among mental health professionals and PCPs hinders action.
• Lack of training of PCPs to identify and treat mental disorders.
• Lack of expert input by psychiatrists into the organization of mental health care on the public health level
• No funding to train PCPs.
• Time constraints limit the curriculum in mental health care in medical and nursing schools.
Patient-related factors
• Patients lack the necessary knowledge to understand that their symptoms are psychiatric.
• Patients fear to seek treatment because of stigma.
Physician-related factors
• Stigma is rampant, and physicians hold negative attitudes towards patients with mental disorders.
• Lack of knowledge to treat complicated psychiatric disorders such as psychotic disorders and bipolar disorder
• Lack of adequate time to treat mental health disorders and offer therapy in the primary care setting
• Lack of financial compensation for the amount of time spent with patients with psychiatric disorders
• Lack of identification of mental disorders in patients presenting with somatic complaints.

The largest epidemiological study of mental health services in Lebanon revealed only a minority of Lebanese people with mental health disorders receive appropriate treatment (Karam et al., 2006). No data exists for emergency treatment and management exists other than restraints known to be used often through use of coercion (Chahine & Chemali, 2009).

Part of the aim of this overall thesis was to impact on this dearth of policy (please see Chapter VI impact adoption section).

c. Local

Local implementation of even national policy is patchy. I am grateful to Steph Sampson (fellow PhD student in University of Nottingham) for use of her pre-publication data for this short section (Bartlett & Sampson, 2020)

Between October and December 2016 Steph Sampson sent Freedom of Information requests to all 243 National Health Service (NHS) Foundation Trusts in England requesting a copy of Trusts' most recent rapid tranquillisation or chemical restraint policies, and then sent in the form of an email directly to individual Trusts. A total of 201 Trusts (83%) responded to the original requests; of these 111 (47%) replied with a copy of their policy attached; six (2%) stated that they had no such policy but consulted relevant NICE guidelines

when required; and three (1%) provided an algorithm or 'holding policy' as opposed to a developed rapid tranquillisation policy. Of the total 120 policies provided by these Trusts, 107 were specific to rapid tranquillisation.

123 Trusts did not provide a policy. Eighty-one (35%) stated that they had no such policy, with seven of these stating that a specific rapid tranquillisation policy was under development at the time of the Freedom of Information request. Finally, 14 Trusts (6%) acknowledged receipt of the request only with no further correspondence, and 28 (12%) did not reply at all. The reasons are not clear why 81 Trusts did not have a specific policy, but reasons for non-return of policies may include: not offering those relevant restraint services, not having a specific rapid tranquillisation policy but a generic 'restraint' policy, definitional differences (one Trust requested a clarification of the meaning of 'rapid tranquillisation'), or failure to develop a policy through oversight or other conflicting time priorities.

In any event local policy – at least in the UK – has greatly complied with that of the national guidance but does still seem to have some way to go before there is a uniform direction for local health care workers.

1.6 Conclusions

Although classifying and characterising aggression/agitation/violence is problematic, by careful consideration of past work it is possible to provide some clarity for working definitions.

Although the causes and association of aggression are multiple and complex, there is good evidence that prevalence in psychiatric settings is high.

Finally, although, this chapter does not attempt a systematic overview of all policy internationally, I have found no example that drifts from the underlying principle of upholding the rights and dignity of the patient, ensuring a patient-centred focus within any incident, and managing the situation by prevention first, de-escalation second and use of coercive methods only as a last resort.

1.7 Coda

In the many reports documenting abuse (Hill, 2012; The Care Watchdog, 2019), impassioned calls for reduction of coercive practices (MIND, 2013), academic documentation of practice (Ewington, 2016) and its refinement (Duxbury & Whittington, 2005), and guidance/policy there remains the on-going plea for more research. The potency of this oft-repeated plea may be diminished by the similar needs from so many other areas

of health care, biases and, perhaps, the conflicts of interest of those making such pleas. However, when the plea is local, un-conflicted and from a grieving family on the doorstep of a coroners court, its urgent relevance hits home (Figure 3 below) ("Inquest family calls for restraint methods inquiry", 2011).

Figure 1.3: ("Inquest family calls for restraint methods inquiry", 2011)

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Inquest family calls for restraint methods inquiry

20 May 2011 Share

The family of a mental health patient who died in a Nottinghamshire hospital has called for an inquiry into restraint methods.

Mr Lovegrove was sectioned under the Mental Health Act

Derek Lovegrove, 38, died at Cedar Vale, an 18-bed hospital in East Bridgford, in July 2006.

The inquest at Nottingham Council House heard Mr Lovegrove stopped breathing after being restrained but a post-mortem was inconclusive.

The jury returned an open verdict but relatives said research was needed.

The inquest was told Mr Lovegrove, who was blind and partially deaf, was a volatile patient with communication problems, often grabbing staff and tearing off clothes.

Different methods

On the day of his death he pulled a worker to the ground.

Another member of staff helped hold Mr Lovegrove down but he stopped breathing shortly afterwards.

A pathologist said he could not rule out that restraint had contributed to the death.

Speaking through their solicitor, the family said there were lots of different restraint methods used in care settings and there needed to be more research into them.

Castlebeck, which runs Cedar Vale, said it would learn lessons from the case.

2. Chapter II – Systematic review of surveys focusing on the management of aggressive behaviour in the psychiatric emergency (and an excursion into bioinformatics)

2.1 Introduction

Chapter I outlined a broad overview of the definition and multiple causes for the aggression seen in psychiatry. It ended with description of treatment approaches and some evidence of global variation. This chapter focuses on the detail of approaches taken to the *management* of this difficult problem worldwide. However, in achieving that aim – via a systematic survey of all relevant surveys – Chapter II, in its first half, describes a brief but important journey into bioinformatics. This original work shows, for the first time, the impracticality of being systematic in summarising surveys. The second half of the chapter does summarise the surveys that were identified - albeit likely to not be a complete sample because of poor indexing.

2.1.1 Aim

The goal of obtaining *all* relevant surveys relating to treatment interventions in emergency psychiatry is to:

- Provide as comprehensive and as unbiased as possible an overview of front-line practices worldwide.

- Locate any data that may be useful to generalise to Lebanese practice
- Learn from surveys of both high and low methodological quality of the past to inform the methods likely to be of value in a survey of Lebanese practice.

Surveys have the capacity to inform the reality of what is happening in a representative proportion of the population - in this case the world - as well as serve as a blueprint that would inform the design of a new survey. Commonly, preceding a pragmatic randomised trial, there is a front-line survey, but, in turn, it is important to ensure that a new survey is indeed necessary by identifying all relevant past work.

2.1.2 What is a survey?

A survey is, ostensibly, one of the most basic of epidemiological methods of research, but remains, if conducted well, one of the most powerful. It has the capacity to inform the observer of really what is happening in defined groups over defined periods. The survey, however, is often confused with the case series. In the latter, a group are audited on certain variables but their relationship to a wider population remains unclear. For example, the interviewer may collect data on 100 people who have experienced treatment of acute aggression. How findings from those people reflect

actual practice may be problematic or impossible to understand. A survey, on the other hand, defines a population to observe - or a stipulated subset of that population – and the time window across which variables will be recorded. Then, for example, if across a week in the life of a Psychiatric Emergency Room, a total of 100 people are treated for acute aggression, then the observer can be more confident that variables collected approximate the real-life experiences of the Emergency Room attendees.

Of course, with both forms of investigation, those not providing data are important sources of bias. However, with the case series, because it was capped at 100 people it is impossible to know if these 100 people are representative. With a survey, however, it is different. In the hypothetical example, although 100 were captured in interview, perhaps a further 30 eligible people refused interview. The survey gives us an opportunity to calculate an accurate incidence rate (130/week) and an estimate of how representative the final sample of interviewees was of the total eligible group.

2.1.3. Inclusion / exclusion criteria

a. Inclusions - surveys

- Recording practice – as advised by overseeing clinicians, or as actually undertaken

    - For people who are aggressive, agitated or violent likely due to psychiatric problem
- In a defined population
- Over a defined period of time

b. Exclusion – case series[1]

- Recording practice – as advised by overseeing clinicians, or as actually undertaken
    - For people who are aggressive, agitated or violent likely due to psychiatric problem
- In an ill-defined population
- Over an unspecified period of time

2.1.4 Critical appraisal of a survey

Because the survey methodology can be defined, critical appraisal is possible. Checklists to guide such appraisal have been developed (Burls, 2014). These all involve consideration of the methodology and, to greater or lesser extents, the application of the findings.

Table 2.1: Critical Appraisal of a survey is taken from Crombie, The Pocket Guide to Critical Appraisal (Crombie & Harvey, 1997). This is the critical appraisal approach used by the

[1] I, however, did include the large POMH-UK case series as it is very large – the likelihood of any validity of a case series being increased by size - and it is local (to the UK)

Oxford Centre for Evidence Medicine, the Dutch Cochrane Centre, the BMJ Editor's checklists and the Evidence for Policy and Practice Information (EPPI) Centre (Crombie & Harvey, 1997).

Table 2.1: Critical appraisal of a survey

Appraisal questions	Yes	Can't tell	No
1. Did the study address a clearly focused question/issue?			
2. Is the research method (study design) appropriate for answering the research question?			
3. Is the method of selection of the subjects (employees, teams, divisions organizations) clearly described?			
4. Could the way the sample was obtained introduce (selection) bias?			
5. Was the sample of subjects' representative with regard to the population to which the findings will be referred?			
6. Was the sample size based on pre-study considerations of statistical power?			
7. Was a satisfactory response rate achieved?			
8. Are the measurements (questionnaires) likely to be valid and reliable?			
9. Was the statistical significance assessed?			
10. Are confidence intervals given for the main results?			
11. Could there be confounding that has not been accounted for?			
12. Can the results be applied to your organization?			

2.1.5 Systematic reviews of surveys

This approach simply applies the principles of good epidemiological techniques in undertaking a survey (good definition of target population and time frame, comprehensive capture of that population, reliable and valid data extraction and synthesis, thoughtful write up). In the case of this

systematic review the 'population' is biomedical literature – specifically surveys of emergency psychiatric treatment. Such surveys of surveys have been undertaken before and provide overviews of practice (Cooper, Browne, McClean, & King, 1983; Huf et al., 2002; Pilowsky et al., 1992).

In the case of a systematic review of surveys the methods of the target studies must be surveys, involving definition of target population, and time period and outcomes are any concerned with the emergency treatment of people in psychiatric care.

2.2 Bioinformatics - Identification of target studies

2.2.1 Background

The methodological identification of specific types of studies is a problem commonly encountered by researchers and Information Specialists. Much has been written about the methodical identification of randomised trials (Corrao et al., 2012), cohort studies (Fraser, Murray, & Burr, 2006) and systematic reviews (Lunny, McKenzie, & McDonald, 2016). Nothing, however, is published on methods for finding surveys – a – perhaps *the* - backbone of epidemiological research. Repositories of search strategies for trials, cohorts and reviews do exist providing helpful searches for specific databases

(Glanville et al., 2008) but no such repository or even single published paper could be identified for surveys.

2.2.2 Aim

To use available biomedical bibliographic databases to systematically identify surveys relevant to emergency management of people who were aggressive and thought to be mentally ill.

2.2.3 Method

A sample of relevant surveys already identified for preparation for a protocol for a relevant trial (Huf et al., 2002) was used as a starting point (Box 2.1).

Box 2.1: Starting points survey

- Binder, R. L., & McNiel, D. E. (1999). Contemporary practices in managing acutely violent patients in 20 psychiatric emergency rooms. Psychiatric Services, 50(12), 1553-1554.
- Cooper, S. J., Browne, F. W., McClean, K. J., & King, D. J. (1983). Aggressive behaviour in a psychiatric observation ward. Acta Psychiatrica Scandinavica, 68(5), 386-393.
- Huf, G., Coutinho, E. D. S. F., Fagundes, H. M., Oliveira, E. S., Lopez, J. R. R., Gewandszajder, M., ... & Adams, C. E. (2002). Current practices in managing acutely disturbed patients at three hospitals in Rio de Janeiro-Brazil: a prevalence study. *BMC psychiatry*, *2*(1), 4.
- Moritz, F., Jenvrin, J., Canivet, S., & Gerault, D. (2004). Conduite à tenir devant une agitation aux urgences. *Réanimation, 13*(8), 500-506.
- Pilowsky, L. S., Ring, H., Shine, P. J., Battersby, M., & Lader, M. (1992). Rapid tranquillisation. A survey of emergency prescribing in a general psychiatric hospital. British Journal of Psychiatry, 160(JUNE), 831-835.
- Rapp, M. S. (1987). Chemical restraint. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 32*(1), 20-21.
- Cunnane, J. (1994). Drug management of disturbed behaviour by psychiatrists. *The Psychiatrist, 18*(3), 138-139.

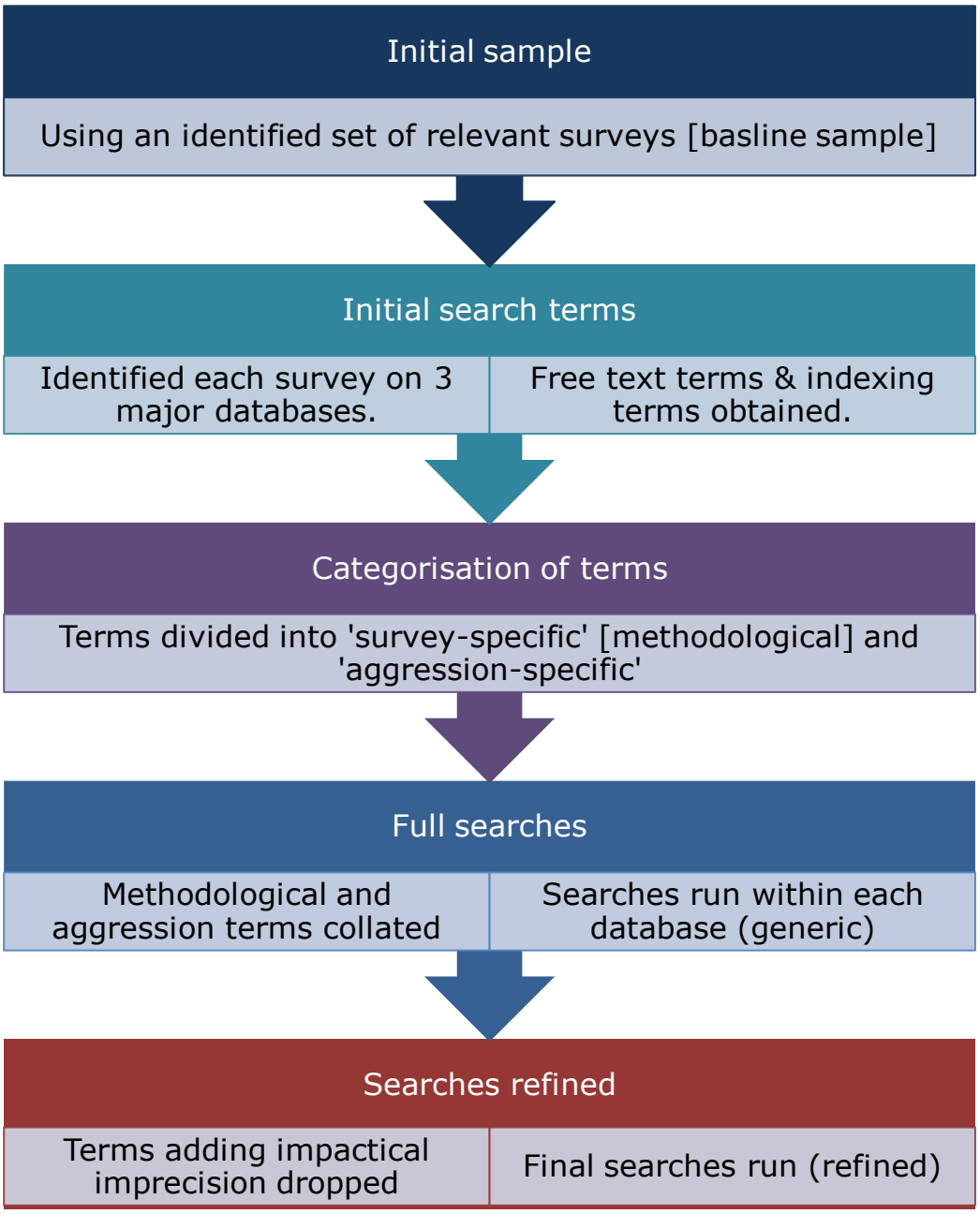
This list could be limited in its thoroughness and certainly is now out-dated but is the only existing one that could be readily identified.

Each survey off the list was identified on two general biomedical bibliographic databases (EMBASE, MEDLINE) and one more that is speciality specific (PsycINFO). Each databases' record of the five surveys was located. Then the content-specific (relating to aggression) and methodology-specific (relating to survey methods) free-text and indexing

terms were highlighted. Free-text terms – those words or phrases in the text of the electronic record within the database (title, abstract) - are common to all databases. Indexing terms, however, facilitate identification of the article and ascribe meaning to the content of the paper using a controlled indexing language. These complex and sophisticated controlled terms are particular to each database. Specialist databases such as PsycINFO can be expected to have more in-depth indexing for the target specialty. The large general databases, however, often lead when it comes to indexing of methodology.

The overall procedure is outlined in Figure 2.1: Identification of target studies.

Figure 2.1: Identification of target studies



The content-specific (Table 2.2: Content-specific terms (i.e. Terms relating to aggression) and methodology-specific terms (Table 2.3: Methodology specific terms) were listed under their respective databases.

Table 2.2: Content-specific terms (i.e. Terms relating to aggression)

	Freetext	Indexing		
		Embase	**Medline**	**PsycInfo**
Binder	TI– Violent AB- Acutely Violent Patients AB– Violent	Violence Emergency ward Emergency health services	Mental disorders Restraint Emergency Services Violence prevention and control Injections/Intramuscular	Patient Violence Psychiatric Hospital Staff Psychiatric Hospitals
Cooper	TI– Aggressive Behaviour AB– Aggression AB– Violent Incident AB– Violent AB– Aggressive AB– Violence	Not Available	Aggression Violence Hospitals, Psychiatric	Aggression Violence Hospitals Psychiatric
Huf	Ti– Disturbed AB– Aggression AB– Violent	Aggression Emergency ward Mental hospital Controlled study Tranquilizing activity Drug efficacy Emergency ward Drug mixture Drug safety	Injections/Intramuscular Drug Protocols Drug Utilisation Psychology Psychiatry/Psychiatric Aggression	Aggressive Behavior Patients Psychiatric Hospitals Psychosis Violence
Moritz	TI– Agitation AB– Restraining AB–Aggravation AB– Sedation	Agitation Emergency Ward Sedation	Aggression Emergency Service, Hospital	Not Available
Pilowski	AB– Rapid Tranquilisation AB– Behavioural Disturbances	Affective neurosis/ Dt [Drug Therapy] Aggression [Side Effect] Diagnosis Drug therapy Intramuscular drug administration Intravenous drug administration Major clinical study Oral drug administration	Aggression/psychology Antipsychotic Agents/administration & dosage/classification/ *therapeutic use Dangerous Behavior Hospitals Psychiatric Injections Intravenous Mental Disorders/*drug therapy/psychology	Aggression Dangerous Behavior Injections, Intravenous
Rapp	TI– Restraint AB– Violence AB– Resisting	Aggression Restraint	Hospitals, Psychiatric Patient Compliance Antipsychotic Agents	Hospitals, Psychiatric Patient Compliance Antipsychotic Agents
Cunanne	Not Available	Not Available	Not Available	Not Available

Table 2.3: Methodology specific terms

	Freetext	**Indexing**		
Huf	TI – "Current Practices" TI – Manag* AB – Surv*	Embase (SH)	Medline (MeSH)	PsycInfo (SH)
		Health Survey; Evaluation; Prevalence; Controlled study; Mental hospital; Clinical study; Patient care; Clinical practice	Clinical Protocols Research Design	Management Epidemiology
Pilowski	TI – Survey AB – Surveys /Surveyed AB – Medical Practice AB – Incidents AB – Frequently	Major clinical study	Surveys and Questionnaires Pilot Projects	Management Epidemiology
Moritz	AB – Management AB – Incidence AB – Frequently	Clinical Protocol Incidence Major Clinical Study	Not Available	Not Available
Binder	TI- Managing TI –Contemporary AB- Survey AB- Practices AB – Structured Interview AB – Frequently AB –Management	Case Management Health survey Clinical Protocol Medical practice	Patient care management Drug administration schedule	Case Management
Rapp	AB – Frequently AB – Survey AB – Prospective AB - Incidence	Incidence	Not Available	Not Available
Cooper	AB – Questionnaire AB – Incidence AB – Prevalence AB – Incident AB – Frequently	Not Available	Not Available	Not Available
Cunanne	Not Available	Not Available	Not Available	Not Available

Then, using the Bolean operator 'OR', the free-text terms were combined. These strings of terms were run over and over dropping terms if they added imprecision. After the initial search whereby all seven surveys were located in all three databases, terms that were imprecise were being removed and rechecked if the terms were uniquely attributed to all surveys thus rendering up the seven surveys until a refined limited number of terms were left for a final search run (simple illustration in Box 2.2).

Box 2.2: Refining a search strategy

SEARCH A [phrase #1] OR [phrase #2] OR [phrase #3] OR [phrase #4]	Identifies 1000 records – including all 'starting point' surveys
SEARCH B [phrase #1] or [phrase #2] or [phrase #3]	Identifies 800 – including all 'starting point' surveys – therefore phrase #4 is redundant
SEARCH C [phrase #1] OR [phrase #2]	Identifies 500 records – but not 2 'starting point' surveys – therefore – in the company of phrase 1 & 2, phrase #3 is necessary

2.2.4 Results

a. The search phrase

Every free text phrase and every index term relevant to the survey methods and aggressive behaviour were harvested from each of the target records available within the databases. Every available phrase, when run within the target database (generic phrase) resulted in prohibitively high hit rates (grossly high sensitivity at cost of specificity).

When refinement of phrases was undertaken using the technique outlined in Box 2.2: Refining a Search Strategy above, the resulting phrases were much simpler, identified all the target studies and many less records. However, the total number of records identified in each database was still very high. The final search phrases in each database were such that there was almost total dependence on the authors using the phrase "survey" in title or abstract. No database had an indexing term for this important type of methodology, with EMBASE being the nearest by having and using the index term 'Incidence/'.

b. Medline

MEDLINE is a biomedical database of 24 million records. The generic methodological terms for 'survey' resulted in 3,600,597 items while the refined methodology terms resulted

in 1,245,338. The generic aggression terms yielded a total result of 742,608 while the refined terms for aggression resulted in 46,427. The combination of generic methodological terms and aggression terms resulted in a total of 194,765. The final refined search of methodology and aggression terms resulted in 8,822 records (please see Appendix A for all index terms).

c. PsycINFO

PsycINFO is a biomedical speciality-specific database of 4.2 million records. The generic methodological 'survey' terms resulted in 953,434 items while the refined methodology terms resulted in 517,376. The generic aggression terms yielded a total result of 208,912 while the refined terms for aggression resulted in 85,812. The combination of generic methodological terms and aggression terms resulted in a total of 58,270. The final refined search of methodology and aggression terms resulted in 16,038 (please see Appendix A).

d. Embase

EMBASE contains 30 million records. The generic methodological 'survey' terms resulted in 10,816,529 items while the refined methodology terms resulted in 2,365,166. The generic aggression terms yielded a total result of 8,663,984 while the refined terms for aggression resulted in

143,610. The combination of generic methodological terms and aggression terms resulted in a total of 7,521,929. The final refined search of methodology and aggression terms resulted in 14,964 (please see Appendix A).

e. Combined

Taking the refined total results from MEDLINE (8,822), EMBASE (24,964) and PsycINFO (16,038) resulted in 39,824 total papers. After running duplicate checks, the number of duplicates was 9,090, which left the final total combined total at 30,734 reports Figure 2.2: Summary of database searching (undertaken 27/1/2017) *Generic ** Refined.

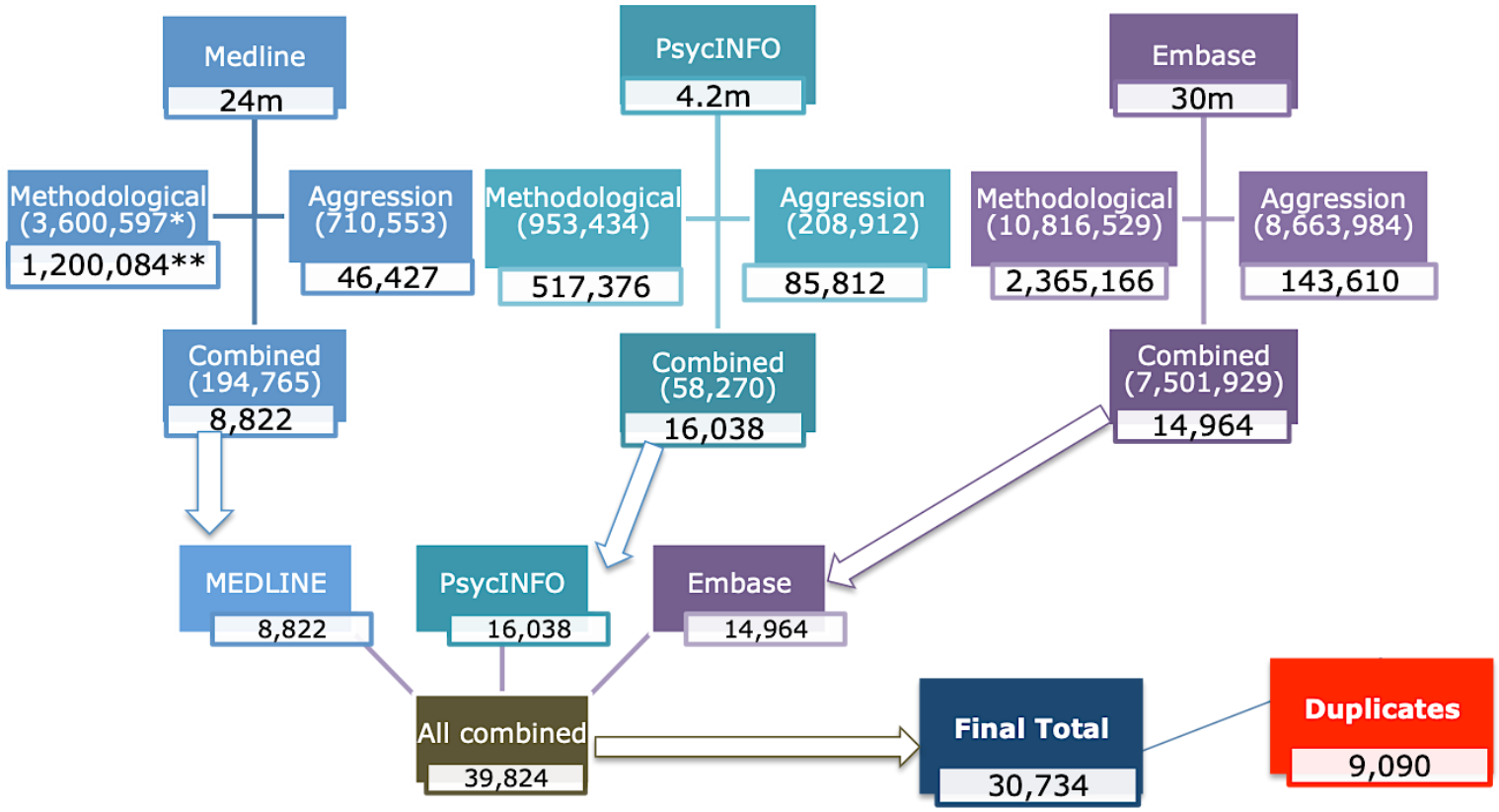


Figure 2.2: Summary of database searching (undertaken 27/2/2017)

f. Endnote

The disappointingly large numbers of reports (30,734) were imported into the reference management software (EndNote). Theoretically, it is possible to manually check the 30,734 reports and extract potential surveys, but time was limited. A judgment-call had to be made. In order to guard against the perfect being the enemy of the good - while remaining systematic in approach - a hierarchical was employed (See Table 2.4: Identifying potential surveys using selected terms of three search categories). This used three search categories; the first was 'Any field', the second 'Title' and the third 'Abstract'. From there, I used both the generic and specific terms - identified by investigation of the initial 7 surveys – and searched each category – essentially as free-text within Endnote. The goal here was to create quick, practical highly sensitive and highly specific combinations so searching within the 30,734 would be rapid and accurate. Table 2.4: Identifying potential surveys using selected terms is ordered by eventual 'value' of the results – not by the order in which they were undertaken. I attempted, perhaps, 50-100 combinations but most resulted in very imprecise identification of very large numbers of reports.

I rated the search strategy as 'OK', 'acceptable' and 'poor' depending on the ratio of the number of results identified to

the number of true surveys located within those results. The numbers identified had to be small, and the proportion high. In addition, duplication of identification within different searches was desirable – giving some support for a theory that the limited sample of true surveys within the greater 30,000 was surfacing with the searches. It remains likely, however, that some surveys within the sample have not been identified. It seems *less* likely, however, that large well-conducted, well-reported surveys have not been found. Beyond the 14th search listed in Table 2.4: Identifying potential surveys using selected terms [((aggression AND managing) ANYFIELD) AND ((treatment) TITLE))] the pain (lack of sensitivity) seemed to greatly outweigh the gain (specificity). In this way fourteen more surveys were added to the initial pool of seven.

Table 2.4: Identifying potential surveys using selected terms

Index used 30,734																						Total search results	Potential surveys identified	Rating
			Any field											Title				Abstract							
	Survey	Aggression	Haloperidol	Lorazepam	Benzo	Managing	Treatment	Violence	Psychiatry	Emergency	Sedative	ER	Rapid	Survey	Treatment	Hospital	Rapid	Aggression	Treatment	Hospital	ER	Survey			
1												✓					✓						12	7	OK
2														✓			✓				✓		4	3	OK
3													✓			✓						✓	4	3	OK
4		✓				✓								✓									3	3	OK
5	✓	✓	✓																				2	2	OK
6	✓						✓		✓	✓				✓									2	2	OK
7														✓		✓	✓						2	2	OK
8		✓		✓										✓									1	1	OK
9														✓				✓	✓				12	4	½
10	✓				✓		✓																9	3	½
11							✓	✓						✓						✓			8	3	½
12	✓										✓	✓											8	3	½
13	✓	✓					✓			✓													15	1	Poor
14		✓				✓									✓								6	1	Poor
Total surveys located: 21																									

2.2.5 Discussion

The results show that survey searching is very problematic because indexing is poor. Authors, journal editors or the databases could greatly improve matters.

Changes in indexing policy within any bibliographic provider do not happen quickly. Free text searches are the most likely way of identifying this type of research for some time into the future so authors and editors could help. The majority of authors did not include the word 'survey' in their title or abstract. There is no indication that editors encouraged embedding the methodological term within the title or abstract. Structured abstracts should improve this situation but both authors and editors should be assiduous about ensuring that the text that the major bibliographic databases freely import contains clear description of methods.

Of the databases, PsycINFO yielded the smallest number of results. It is the smallest database, being the only one of the three that is specialist. The indexing for the topic (aggression) was better than the other two databases, which would fit with the specialist nature of the database, but the indexing for methodology (survey), worse. While EMBASE and MEDLINE did have more methodological indexing terms only EMBASE had one that was really likely to highlight surveys (Incidence/).

The great size of these two general databases, combined with the less refined indexing of the topic of aggression leads to disappointingly high yields of limited specificity and unknown sensitivity. Of the original surveys used, only Huf (Huf, da Silva Freire Coutinho, et al., 2002) 'survey' as an index term so, ironically, that potentially useful term had to be deleted from refined searches. When over 30,000 potential surveys were located across three great databases, even with a search that was refined, new surveys had to be identified using a pragmatic approach while remaining systematic. This was possible but the confidence in the completeness of results is not great.

2.3 Systematic review of the 21 surveys

2.3.1 Background

After the initial list of surveys were discovered and assessed, a systematic appraisal of the surveys followed in order to critically summarise the research.

2.3.2 Aim

- To critically appraise all surveys relevant to treatment of people who are aggressive/agitated/violent thought to be a result of what is considered a psychiatric problem.

- To appraise these studies using a recognised checklist and rating standard.

- To learn from surveys of high quality to inform the design of a Lebanese survey.

2.3.3 Methods

All surveys were listed on Table 2.6: Critical appraisal of surveys and separated into two broad categories - surveys of *practice* and surveys of *clinicians' opinions* as well as their year and country of origin. Using a recognised checklist for critically appraising surveys (Crombie & Harvey, 1997) all quality questions were answered by using three categories:

'Yes'		2 points
'Maybe'		1 point
'No'		0 points

(Table 2.6: Critical appraisal of surveys).

By allocating scores to each answer the surveys then could be listed in Appendix B which is a systematic review of surveys according to percentage of maximum (24 points) along with the relevant qualitative and quantitative data. Where doubt arose, JD asked supervisor CEA to adjudicate on scoring.

Table 2.5: Inclusion/exclusion criteria

Inclusion	Exclusion
Surveys	Any other epidemiological design
Addresses treatment interventions in the emergency psychiatry	General hospital emergency intervention i.e. geriatric patients suffering from dementia

2.3.4 Results

From Table 2.6: Critical appraisal of surveys we see how the surveys were divided almost equally into those that focused on asking clinical opinion of *what should happen in the emergency* and those that *actually monitored practice* during those times. The exceptions were Allen and Currier (2004) and Chan, Knott, Taylor, and Kong (2011), which surveyed both opinion and practice. Using the crude scoring system, it became clear that several of the studies were of superior quality (Those over 80%) (Bervoets et al., 2015; Chan et al., 2011; Huf, da Silva Freire Coutinho, et al., 2002; Pilowsky, Ring, Shine, Battersby, & Lader, 1992b). Many studies failed to pick up points were sampling biases were unclear or unaccounted for and confidence intervals (ranges of likely values for the population parameter) were not reported.

When it comes to overall content of the surveys there is no accepted way of weighting results of this type of methodology,

therefore they are presented individually in Appendix B. The quality rating is copied from Table 2.6: Critical appraisal of surveys and additional information entered.

It is difficult to pick out any key result from Appendix B apart from the wide range of choices that are available worldwide. Clearly the two great classes of drugs are favoured – antipsychotics (coded as 'A') and benzodiazepines (coded as 'B'). Of the 16 different antipsychotic medications haloperidol seemed favoured and of the benzodiazepines the short acting lorazepam was commonly employed. Combinations of drugs – although commonly reported in Brazil – did not seem prevalent in these surveys.

Regional differences are suggested by the use, for example, of the benzodiazepine midazolam in Australia and the antipsychotic clotiapine in Belgium. There were no surveys covering practice or opinion within the Middle East.

The POMH-2017 (POMH-UK, 2017) is worth particular note as it is recent and large. Strictly speaking this work is not a survey as it recruited a number of UK regional Trusts, which agreed to come on board and there is no clear stipulation of what proportion of Trusts did not. How this sample represents the UK is, therefore, unclear. In addition, the time frames for different Trusts varied and recruitment did not seem clearly

capped by time – making POMH-2017 (POMH-UK, 2017b) more of a large case series or audit than a true survey (hence its relatively low critical appraisal scoring in Table 2.6: Critical appraisal of surveys). However, POMH-2017 (POMH-UK, 2017b) was large and this probably should give its findings some more authority than the several much smaller studies.

Table 2.6: Critical appraisal of surveys

Appraisal questions	Clinician Opinion											Surveys of Practice									
	United Kingdom						U.S	Multiple African Countries	Belgium	U.S	Australasia	United Kingdom				Canada	Ireland	France	Australasia	Brazil	Multi-National
	Cunnane-1994	Thacker-1996	Simpson-1996	Reid- 2003	Antwi- 2006	Pereira- 2006	Binder 1998	Bawo- 2011	Bervoets-2015	Allen -2004	Chan- 2011	Cooper-1983	Pilowski-1992	Haw-2012	POMH-2017	Rapp- 1986	Mannion-1997	Moritz-1999	Cannon-2001	Huff-2002	Lepping- 2003
1. Addressing a clearly focused question/ issue?	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
2. Study design appropriate?	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
3. Method of selection of subjects clearly described?	□	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	□
4. Could the sampling introduce (selection) bias?	□	□	□	□	□	■	□	□	□	□	□	□	□	□	□	□	□	□	□	■	□
5. Was the sample of subject's representative with regard to the population to which the findings will be referred?	■	■	□	□	□	■	□	□	■	■	□	■	■	□	■	■	□	□	■	■	□
6. Was the sample size based on pre-study considerations of power?	□	□	■	□	□	□	□	■	■	■	□	□	■	□	□	□	□	■	■	■	□
7. Was a satisfactory response rate achieved?	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
8. Were questionnaires likely valid and reliable?	□	■	■	■	■	■	■	■	■	■	■	□	■	■	■	□	■	■	■	■	□
9. Was the statistical significance assessed?	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	□	■	■	□
10. Are confidence intervals reported?	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	□	■	■	□
11. Could there be unaccounted confounding?	■	□	□	□	□	□	□	□	□	□	□	□	□	□	□	■	□	□	□	□	□
12. Can the results be applied to your organization?	□	□	□	□	□	□	□	□	■	□	■	■	■	□	■	□	□	■	■	■	■
Total percent of maximum 24 points	**54**	**66**	**75**	**62**	**62**	**45**	**62**	**66**	**83**	**79**	**83**	**66**	**83**	**62**	**70**	**58**	**62**	**79**	**75**	**87**	**66**

2.3.5 Discussion

It remains unclear if the 21 surveys (Allen & Currier, 2004; Antwi et al., 2006; Bervoets et al., 2015; Binder & McNiel, 1999; Cannon, Sprivulis, & McCarthy, 2001; Chan, Knott, Taylor, & Kong, 2011; Cunnane, 1994; Haw, Stubbs, & Gibbon, 2013; James, 2011; Lepping, 2013; Moritz, Jenvrin, Canivet, & Gerault, 2004; Pereira, Dawson, & Sarsam, 2006; Rapp, 1987; Reid & Hughson, 2003; Simpson & Anderson, 1996) really represent the totality of relevant evidence of this sort. It would seem unlikely, however, that large, well-reported surveys have been missed by the searches, but this does remain possible. The critical appraisal tool is limited with several open-ended questions that are difficult to provide definitive answers for. It is possible that a different appraiser – albeit that I had supervision for problematic decisions – would have come to different scorings. Having said that, however, the findings of the scoring did – subjectively - feel correct. The studies that had seemed better conducted, when more 'objectively' appraised – did score better. However, application of this scoring into consideration of the overall findings is problematic. Even in highly evolved methods of meta-analysis of trials and cohorts weighting of results by quality largely remains qualitative, whereas within meta-analyses size and number of events does matter as regards weighting. I have

not synthesised the data across the surveys but in consideration of the findings it would seem reasonable to note size as well as critical appraisal scores.

Clearly in both clinicians' option and practice, the management of aggression in the emergency often necessities use of an antipsychotic or/and benzodiazepine drug. These are administered orally or, more commonly, IM or even IV. The global variation in which choice of drug to use suggests that practice is directed by forces other than overwhelming evidence, for if the latter were the case more uniformity of approach would be expected. Newer generations of drugs are being used but, even in rich countries, older drugs predominate. No survey covered the region of the Middle East.

2.4 Conclusions from the overview of surveys

Frequently health services research starts with overviews of practice. The unique early work within this chapter suggests that a systematic approach to identification of surveys is, currently:

- Very problematic
- Likely to yield results about which it is impossible to be confident that they represent an unbiased sample of the total 'population' of studies; and

- Could be greatly improved by inclusion of the methodological description (e.g. 'survey') in the titles.

The 21 surveys identified were of variable quality and size. Although there is a broad consistency in pharmacological approach – with use of antipsychotic drugs or benzodiazepines – the variation of choice is considerable. Part of the variation seems regional. I found no survey of practice or opinion in the Middle East.

For Lebanon, an evaluative study of the effects of treatments used in everyday care can only be undertaken if:

- The routine treatments are known,
- There is an evidence-gap regarding those treatments, and
- Everybody wants an evaluative study to happen.

Chapter III describes the survey of emergency treatment in Beirut in order to clarify routine practice – and begin to predict recruitment for a potential evaluative study. Chapter IV then investigates the levels of evidence for treatments I found to be used in Beirut.

3. Chapter III- A survey of the treatments that are currently locally recommended and/or used in the Lebanese emergency psychiatric setting

3.1 Background

From the identification of surveys of clinicians' opinions and clinicians' practice in Chapter II it was clear that there was no global uniformity of opinion or practice. It, therefore, was important to survey opinion and treatments in Lebanon. This would serve to highlight where Lebanon stood in relation to other surveys and introduce the idea of this type of evaluation to local services and provide background for possible investigation into the effects of their approaches.

3.1.1 Aim

- To discover what the local clinicians of Beirut recommend for treatment techniques in the aggressive psychiatric emergency;
- To survey what treatment techniques are really used in front-line practice in one large Beirut hospital;
- To act as a foundation of an exploration of any evidence-gaps on local treatments in Lebanon (Chapter 4); and
- To facilitate the design of a pragmatic randomised trial by gaining:

- intimate knowledge of pathways of care in front-line care of this hospital
- trust of as many relevant clinicians as possible, creating an *espirit de corps* to carry into a trial.

3.1.2 The rationale for this survey

A pragmatic randomised trial is an evaluative study that interferes minimally with every day care (Hotopf, 2002). People recognisable in daily care will be allocated to [under-evaluated] routine treatment approaches and outcomes collected that are also hoped to be part of everyday data collection. However, for all this to happen several foundations have to be put in place. Everyday care – so familiar yet often so under-researched – must be thoroughly investigated.

Past surveys have not sufficed in providing knowledge of the region's practice. The survey I identified which was physically nearest to Lebanon was from France (Moritz et al., 2004). In Beirut, it was unclear who presents for management of their psychiatric emergency and who accompanies them and in what circumstances. It is also unclear what treatments are recommended or really used in front line care – whether these are already well known or idiosyncratic to Lebanon. Finally, it was not fully understood what outcomes are recorded by the staff and exactly how this is undertaken. This final set of

knowledge serves to inform about what is felt to be important by the staff and gives valuable insight into the quality of these routine data.

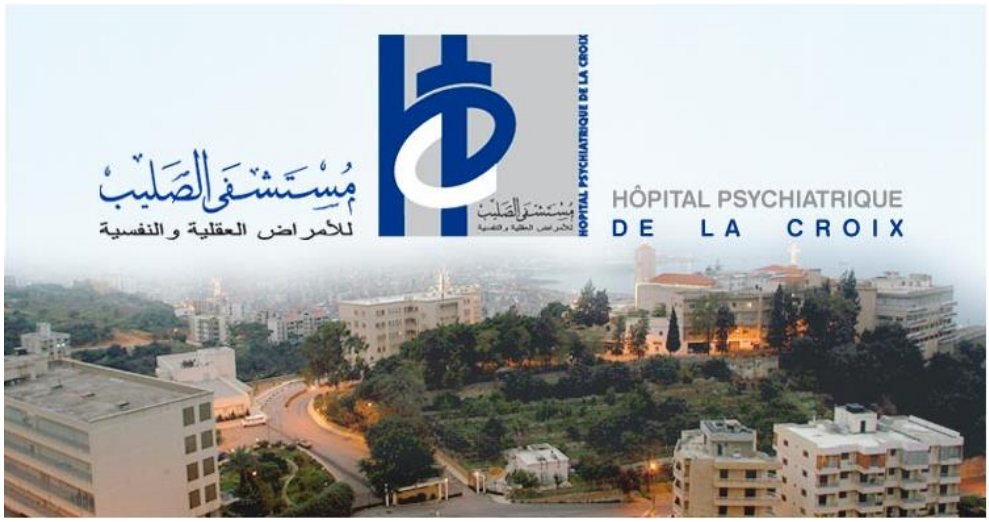
The survey necessitated getting approvals, gathering information from all relevant staff and gaining their trust. The write up and dissemination of the survey, authored by all contributing staff, was important as a vanguard for, potentially, the more important study – the pragmatic trial.

3.2 Methods

3.2.1 Site

The survey was being carried out in 'Deir Salib Hôpital Psychiatrique De La Croix' (http://www.hopitalpsychiatriquedelacroix.org.lb/). This is the largest - and only - public psychiatric hospital in Lebanon (total population 6m). The Lebanese health system is diverse with many providers. Those with wealth may fly out or use the private hospitals. This probably accounts for 10% of the population. Those with affiliations to the military have veterans' institutions (40%) with the remaining 50% of the population using the public hospital. Deir Salib Hôpital Psychiatrique De La Croix admits from across the country making it a good representation of psychiatry in Lebanon.

Figure 3.1: Deir Salib Hôpital Psychiatrique De La Croix



The hospital consists of nine hundred rooms and permits both acute and chronic patients; males and females, children, adults and the elderly. There are three buildings that make up the entirety of the hospital with each building containing wards where patients are kept segregated by sex, disorder, insurance and severity. For example, the first building is Saint Jacques, which consists of five floors each with its own ward. The first floor (Saint Jacques Ward 1) admits only women. The second floor (Saint Jacques Ward 2) admits only men. The third floor (Saint Jacques Ward 3) also only admits men. The underground floor S1 ward known as 'Reine' only admits women. The fourth floor (Saint Jacques Premium Ward) admits patients with high quality private insurance. The second building is known as 'Saint Michel', which contains only women – usually with chronic illnesses. The third building is known as 'Notre Dame' and contains only male patients with

chronic illnesses. In the hospital, there are a total of eight clinicians – seven who are qualified psychiatrists and one who is specialised in family medicine.

3.3 Aim

To survey the opinion of attending clinicians on how acute aggression should be managed and to survey actual clinical practice.

3.4 Ethics

These surveys were carried out after (1) gaining ethical approval from the University of Nottingham specifically the Division of Psychiatry and Applied Psychology in the School of Medicine and are overseen by the Faculty of Medicine & Health Sciences' Research Ethics Committee. The reference number granted after approval was 242. Application was undertaken in accordance with The University of Nottingham's Code of Research Conduct and Research Ethics (2016). And (2) this also gained approval from Deir Salib Hôpital Psychiatrique De La Croix's Director Mère Arze Gemayel through the consultation of the Hospital's Research Director Dr. Hallit.

3.5 Timing

The survey was from July 3rd, 2017 to August 3rd, 2017.

3.6 Consent

Consent forms were not given to patients but to attending clinicians detailing information about the purpose of the study, about procedures, the benefits and risks of participating, an explanation how to acquire results of the research and contact information of researcher.

3.7 Forms

3.7.1 Clinician's opinion

The Clinicians' form found in Appendix C, asked clinicians' opinions on which intervention techniques should be used when treating an agitated patient. There was no limit on intervention options. The simple form also gathered information on the time period the clinician had been working in mental health as well as how often does he/she treats agitated patients (See Appendix C).

3.7.2 Clinical practice

Form 2 in Appendix C was used to record practice for every episode of emergency management within the hospital. One form for each agitated episode. This form was also simple and quick to complete. The Unique ID was assigned to every patient, and details of the ward in which the patient was placed in order to assess if the patient was thought to be new or someone with chronic illness. A suspected cause was noted, and a diagnosis. In other similar surveys the initial diagnosis made in the first few minutes of the encounter remained stable over time (Huf et al., 2002; Pilowsky, Ring, Shine, Battersby, & Lader, 1992). Age and sex were included. The 'Presentation' variable recorded how the person arrived – via the family, authorities, friends, by themselves or 'others'. The

form also recorded if the patient was restrained *before* admission and whether the patient received treatment before admission. Past surveys had not included these questions that may have a strong impact on intervention techniques when the patient is admitted in the emergency room. Finally, the medications administered to the person were then listed to see what was given in practice (See Appendix C).

3.8 Procedures

3.8.1 Form 1 (Clinician's form)

The hospital's research director (SH) sent the clinician's forms via email. Three were sent back completed during the first week. During the second week, the researcher (JD) attended clinics of two additional clinicians who completed the form on the spot. The remaining two psychiatrists were unable to fill out the form with one citing that he spends too much time outside the country therefore felt his input would not benefit the study and the other was unreachable by email, phone or clinics during the one-month study period.

3.8.2 Form 2 (Emergency episode form)

Data were collected in the three main hospital wards (St. Michel, St. Jacques and Notre Dame) throughout the one-month trial period by the researcher. The three main hospital wards contain patients while other buildings in the hospital

include the administrative branch where patient files are kept and visiting hours are scheduled, a church for Sunday mass and the hospital's lecture hall where presentations and lectures are held. When patients are admitted – either new or recurring - they must be presented through the administrative branch. After a patient is admitted, his/her file is registered into the hospital's system computer that sends an email to all the hospital's residents, staff and clinicians including the researcher. Staff was well informed by the Director of Research regarding the study therefore staff recorded agitated episodes in the survey provided by the researcher even if the researcher was not present during certain hours or was already surveying another incident in another ward. In this way, it was hoped no episodes within the month were to be missed.

The survey form was filled out by attaining the intervention treatments from patients' case files during and after agitated episodes. All was undertaken under supervision of the attending clinician, usually with the chief nurse of the ward floor present. If the patient continued having agitated episodes during the day, one form covered the period until tranquilisation was achieved. If the patient had one agitated episode and rapid tranquilisation was achieved on the same day but another agitated episode occurred the day after, this

counted as a separate episode. One form was filled out per episode. After every form was completed, a unique ID was presented to each individual to guarantee confidentiality.

3.9 Results

3.9.1 Clinicians

A total of seven psychiatrists were given the survey of opinion with five successfully completing the survey. Two were unable to fill out in the given time frame therefore their data are not included in the analyses (four of five were interested in seeing the results of the survey results; one preferred to remain anonymous). All psychiatrists were selected on the basis of being employed in the hospital of Deir Salib. The eighth clinician who specialised in family medicine did not want to partake in the survey as he cited that he does not treat agitated patients.

3.9.2 Clinicians' responses

Five of the psychiatrists completed the survey (See Table 3.1) One psychiatrist was unable to fill out the survey citing being out of the country too often meant his input would not qualify as valid representation to the hospital while another psychiatrist was unable to be reached via phone, clinics or e-mail. The family medicine clinician cited he does not meet with

agitated patients nor administers rapid tranquilisation to his patients therefore not fitting the requirements of the survey.

Table 3.1: Background of clinicians

		Frequency	Percent
How often do you treat a person for aggression?	Daily	2	40.0
	Weekly	2	40.0
	Monthly	1	20.0
	Total	**5**	**100.0**
Ward of work	Notre Dame	2	40.0
	St. Jacques	1	20.0
	St. Michel	2	40.0
	Total	**5**	**100.0**
Period of work in mental health (years)	7	1	20.0
	10	1	20.0
	13	1	20.0
	19	1	20.0
	30	1	20.0
	Total	**5**	**100.0**

3.9.3 Clinicians' opinion of what interventions should be used

Psychiatrists suggested three broad categories of intervention - colour coded in Table 3.2: Data results of Clinicians' Opinions – non-physical; medication, and restrictive. All psychiatrists' first line of intervention was non-physical (non-pharmacological) preferring verbal intervention. Thereafter, as can be seen within Table 3.2, there was a drift to use of oral medication followed by intramuscular (IM) delivery choices. Clinicians tended to not be too specific about which oral medication to choose and IM was usually the latter choice. The two IM treatments mentioned were haloperidol and zuclopethixol acetate. The less experienced psychiatrist

seemed to suggest moving towards restrictive interventions faster than the others.

Table 3.2: Data results of Clinicians' Opinions

Psychiatrist	Experience (years)	Frequency of treating emergencies	Intervention						
			#1	#2	#3	#4	#5	#6	#7
1	19	Daily	Verbal Intervention	Propose tranquilising tablet	Propose IM treatment	HPC IM	Physical Restraint	Physical Restraint +Chemical Restraint	Zuclopenthixol IM
2	7	Weekly		Pharmacological Intervention	Seclusion Room	Physical Restraint			
3	13	Daily		Rule out medical causes	Therapeutic Intervention	Refer to psychotherapy	Assess risk of aggression	HPC IM	
4	10	Weekly		Propose tranquilising tablet	Attain approval from parents	HPC IM			
5	30	Monthly		Give time for patient to calm down	Olanzapine				

Colour key

Non-physical		Medication	Oral	IM	Restrictive	

3.9.4 Clinical practice

a. Patients' background and admission data

A total of 28 patients (39 episodes) were included in the one-month survey of practice (1.26 people/day required rapid tranquilisation). All were adults of Lebanese nationality. The study excluded children (<18) and the elderly (>65). Eligible participants were selected on the basis of being admitted to the psychiatric hospital and having an agitated episode that required rapid tranquilisation.

Most patients were male, in their early 30s, and presented with their families. In a few instances restraints were used before admission (7%) and people had already received some sort of medical intervention (10%) (Table 3.3).

Table 3.3: Background of episode

Sex	**Male**	**Female**			**Total**
	25 (64%)	14 (36%)			39 (100%)
Age	**Mode**	**Mean**	**Range**		
	31 (n=6)	33 (SD 8.9)	18-58		
Presentation	**Families**	**Authorities**	**By themselves**	**Other**	**Total**
	26 (67%)	3 (8%)	4 (10%)	6 (15%)	39 (0100%)
Restraints before admission	**Yes**	**No**			**Total**
	7 (18%)	32 (82%)			39 (100%)
Given treatment before admission	**Yes**	**No**			**Total**
	4 (10%)	35 (90%)			39 (100%)

Of the three admission wards St. Jacque had the highest frequency of agitated episodes (n=18). There were 1.26 episodes per day with a range of 1-12. The commonest day of episode was Monday tailing off by Friday and the end of the week.

Taken alone, bipolar disorder was the most frequent single diagnosis (n=16) but the collective schizophrenia-like illness (schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic episode) totalled 18 of the 39 episodes.

Table 3.4: Episode data

Ward	Saint Jacques	18 (46%)	**Total**
	Notre Dame	12 (31%)	39 (100%)
	Saint Michel	9 (23%)	
Day	Sunday	1 (3%)	
	Monday	12 (30%)	
	Tuesday	9 (23%)	
	Wednesday	6 (16%)	
	Thursday	7 (18%)	
	Friday	2 (5%)	
	Saturday	2 (5%)	
Frequency	Range	1-12/day	
Diagnosis	Schizophrenia	13 (33%)	
	Bipolar Disorder	16 (41%)	
	Substance use	5 (13%)	
	Schizoaffective Disorder	1 (3%)	
	Brief Psychotic Disorder	2 (5%)	
	Delusional Disorder	2 (5%)	

b. Interventions used

Table 3.5 includes the interventions used in the 39 emergency episodes.

i. Verbal

Every clinician had suggested that verbal interventions should be first line. The survey was designed to encourage recording of both drug and non-drug approaches. However, from the data reported non-pharmacological intervention options were minimal consisting of verbal command and straitjacket. In the entirety of the study, verbal command was reported as being used only once as a first line of treatment.

ii. Medications

All 39 agitated episodes received a first line treatment, 25 (64%) received a second line intervention, 14 (36%) a third, 8 (21%) a fourth, 7 (20%) a fifth and just 1 (3%) a sixth line intervention. All drug interventions were given intramuscularly (IM) when patients were agitated and requiring rapid tranquilisation. There was no evidence that an oral option was given or offered – contrary to the clinician's opinion expressed in Table 3.2.

The most commonly used first and second-line drug treatment was diazepam. This IM drug, known for causing residual pain at the site of injection and being erratic in its absorption (Mehta, 2005; Von Dardel, Mebius, Mossberg, & Svensson, 1983), was the most commonly administered single drug intervention (total n=16). The second most used first-line intervention was a mix of chlorpromazine, promethazine and haloperidol. This mixture, called "HPC" by the hospital (C denotes chlorpromazine), is, according to hospital staff, the preferred 'SOS' treatment. It was used a total of seven times as first line treatment but, over the whole survey it was the most commonly employed rapid tranquilisation (n=18). The third most used was a haloperidol promethazine mix – four times as a first-line intervention.

The remaining drugs were benzhexol (an anticholinergic drug used to offset acute movements caused by antipsychotic drugs), or antipsychotics (chlorpromazine, clozapine, haloperidol, olanzapine, promethazine, zuclopenthixol) or benzodiazepines (diazepam, lorazepam) either used as sole treatment or in combinations.

Table 3.5: Intervention order

		First	Second	Third	Fourth	Fifth	Sixth
Non-drug interventions	Verbal Command	1					
	Strait jacket	6	2			1	
Drug interventions (all IM)	Diazepam	8	5	2	1		
	Haloperidol + Promethazine + Chlorpromazine	7	5	4	1	1	
	Haloperidol + Promethazine +/- Benzhexol	4	4				
	Chlorpromazine + Lorazepam	2					
	Lorazepam	2	2	1			
	Zuclopenthixol + Promethazine	2				1	
	Chlorpromazine	1	3	3	2	1	
	Chlorpromazine + Promethazine	1					
	Diazepam + Lorazepam + Promethazine	1					
	Haloperidol	1					
	Haloperidol + Promethazine + Chlorpromazine + Lorazepam	1					
	Olanzapine	1					
	Zuclopenthixol	1				1	
	Promethazine		4	1	4	2	1
	Clozapine		1				
	Benzhexol			3			
Total		**39**	**25**	**14**	**8**	**7**	**1**

iii. Survey Results of Clinical Practice

a. Restrictive

Although from the reported preferences of the clinicians restraints were an available option (Table 3.2: Data results of Clinicians' Opinions), in reality, only straitjackets were employed.

Figure 3.2: Four-point restraint

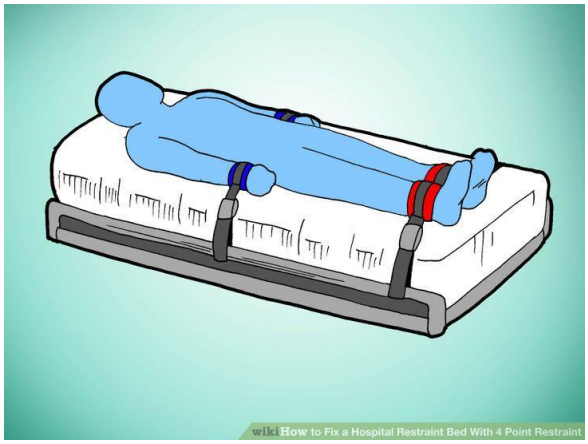


Figure 3.3: Straitjacket

Clinicians had stated that restriction by use of restraints should be an option taken at least fourth after other measures. In reality the straitjackets seem to have been used as first line six times, and second line two (Table 3.5). In

totality, the strait jacket ranked third most used intervention – both non-drug and drug intervention in the entire survey. Seclusion does not seem to have been used despite being one option suggested by the survey of clinician's opinion.

3.10 Limitations

There are limitations to these surveys. They were short and small. Not all clinicians participated, and the simplicity of the form may have lost valuable detail. On the other hand, it seems unlikely that the clinicians that were unable to participate would have had radically different opinions. Perhaps more pushing of the clinicians to give specific choices of approach, or a more structured questionnaire, would have provided more useful information. These are not all the relevant clinicians in Lebanon, but they are the majority that provide this type of public service for the small population of this country.

For the survey of practice, a longer period of observation would have allowed study of more episodes and expression of findings with more confidence. Time and resource were limited and there was already some consistency in the findings of practice. It would have been more informative to know the success of each treatment given, nurses' opinion, patients opinion, adverse events and progression through care. These

are all important variables that were not collected. The purpose of the study was, however, to give grounding in the reality of care in Lebanon and to prepare for evaluation of this care, if indicted, within a randomised study. In this, it is thought the surveys were successful.

3.11 Discussion

This was the first study of its kind in Lebanon to survey treatment options of both clinicians' opinions and practice in this difficult emergency situation. Out of necessity, it was small and short, but its findings are not really different to what has gone before. Few studies have undertaken parallel surveys of clinician's opinion alongside what happens to patients in their care. The survey of the doctors in Lebanon reported here was limited but suggested what is suspected from other work (Bervoets et al., 2015; Binder & McNiel, 1999; James, 2011; Pereira et al., 2005; Thacker, 1996) – that desired practice is not really what happens on the front line.

As regards that clinical front line, the age, sex and likely diagnosis of people presenting in this situation seems broadly similar to what is known from other surveys (see Appendix B). Perhaps the exception is the absence of people with the diagnosis of some sort of personality disorder. The latter is not a diagnosis that is routinely recorded in Lebanon so the figures

reported in Table 3.4 may be under-representative of this diagnosis. It is also possible that people who presents at the hospital are, in effect, pre-screened by the families, and community services to really be only those with functional mental illnesses.

How the person presented was recorded in this survey for a variety of reasons. First, it gives a basic impression on how culture plays a role in the Lebanese setting. Second, what happens before rapid tranquilisation is given is important – treatment choices may change depending on whether the patient was administered a pharmacological drug before admission as seen in Table 3.3 though the medications were not listed in the interventions due to uncertainty what the patient was given. Other surveys, to the best of the authors' knowledge, have not recorded what medication was given prior to presentation. Although difficult to attain, it is a strong confounding variable that influences overall result. Finally, it is important that this clinical detail is understood before the design on any prospective trial. Seven people were placed in physical restraints before admission, but data were not specifically recorded in hospital notes. When brought by police, handcuffs were used as a physical restraint, while a straitjacket was used if hospital staff brought in a patient. Four patients were given some form of medical treatment before

admission, which lead to two patients having at least five medication interventions.

The results for the survey of practice yielded four main intervention options. For the non-pharmacological interventions, the straitjacket was used eight times (20% 95% CI 11-36%). This survey did not have the details of its implementation, how long it was employed, the result of its use and if it caused adverse effects. Use of this approach has not been the study of much scientific enquiry and it is clearly a commonly used way of rendering the person safe in Lebanon.

Nearly half (49% 95% CI 34-64%) of first line treatments were either diazepam or a haloperidol plus promethazine mix (with a proportion of the latter having additional chlorpromazine). When non-pharmacological approaches are removed this proportion rises to 59% (95% CI 42-75%). The most common first line sole drug treatment for rapid tranquilisation in this survey was intramuscular diazepam (20% 95% CI 11-36%). This treatment is known to have erratic absorption and cause residual pain at the injection site (Mehta, 2005; Von Dardel et al., 1983). The first line use of diazepam was similar to the UK survey of the early 1990s (Pilowsky, Ring, Shine, Battersby, & Lader, 1992) but this now seems to have been eclipsed in the UK by lorazepam (POMH-UK, 2017). The haloperidol plus promethazine mix was used

11 times first line (28% 95% CI 17-44%) but in seven Instances, additional chlorpromazine was added (18% 95% CI 9-33%). This mix (HPC) was the hospital's main SOS treatment option for rapidly tranquilising agitated patients and here, clinical practice does broadly concur with the opinion of the attending clinicians. This [likely potent] mix was also employed in Brazil: 7%, (Huf et al., 2002).

Forty percent (41% 95% CI 26-58%) of drug treatments were given only once or twice first line. Various combinations of chlorpromazine, diazepam, haloperidol, lorazepam, olanzapine, promethazine and zuclopenthixol were used with no clear indication from the survey sheet why these were chosen as opposed to the diazepam or haloperidol/promethazine +/- chlorpromazine mix. This proportion of 'various available variations' is a similar to that seen in other surveys and is likely to be the result of a combination of the expression of clinical freedom and clinical judgement.

3.12 Conclusion

In Lebanon, this small, short, imperfect survey of clinician's opinion and practice, in keeping with other work from across the globe, suggests that what clinicians hope is undertaken in the emergency room is not necessarily what happens. This

survey also suggested some consistency of approach in Lebanon – partly out of necessity (there are limited approaches to take), but also partly out of clinician choice. Experienced clinicians in Lebanon, like the UK, the USA and many other places, are repeatedly, routinely, using effective treatments robust for managing people who display an aggressive episode - including a combination of HPC seen only in Brazil before. Whether these particular treatment approaches, like for many places in the world, are poorly supported by evidence from high-grade evaluative studies is the topic of Chapter IV.

4. Chapter IV- Systematic overview of relevant trial-based evidence

4.1 Background

Chapter I summarised literature around the issue of aggression in psychiatry and its causes. Then Chapter II attempted a systematic review of *surveys* of management of aggression – both surveys of *clinician's opinions* of what should be done in the emergency situation as well as surveys of the *actual practice* in the psychiatric emergency room. This illustrated diversity of opinion and practice. Subsequently Chapter III, using Chapter II as a reference, reports a new survey of opinions and everyday practice in Lebanon.

Just as Chapter III used its proceeding chapter as a reference point, Chapter IV will build on the findings of the Lebanon survey and present brief overview summaries of the best available evidence from up-to-date systematic reviews of randomised trials of the treatments that we now know are relevant to everyday practice in Lebanon.

4.2 Systematic overview

A systematic overview is a systematic review *of systematic reviews* (Smith, Devane, Begley, & Clarke, 2011). Systematic overviews are best designed for integrating relevant data from existing systematic reviews or meta-analyses to help make

better decisions, deliver clinical decision makers with the evidence they require when there are too many systematic reviews for them to keep up with for an intervention and finally, when there needs to be a rapid evidence synthesis for decision-makers but higher quality evidence is required due to limitations of the rapid review methodology (Aromataris et al., 2015).

As mentioned above, the treatment options and interventions in the Lebanese psychiatry emergency setting is now known (Dib et al., 2018). The intent of this systematic overview is to include systematic reviews or meta-analyses and examine only the highest quality of evidence available relevant to the practice we now know is prevalent in Lebanon. The aim is not to repeat the searches, assess study eligibility and assess risk of bias of studies already included in up-to-date high-quality reviews but rather provide an overall picture of their findings (Coenen et al., 2018). Where reviews are not up to date, however, supplementary searches for relevant evidence is undertaken.

4.3 Methods

4.3.1 Overall

High-grade reviews relevant to Lebanese practice will be sought and their Summary of Findings tables extracted and

compiled into one final overview summary table. Searches will be undertaken for new trials relevant to the comparisons within the high-grade relevant reviews to ensure that the information within these reviews is not out-dated.

4.3.2 Cochrane reviews

Cochrane *reviews* will be used as the starting point for best trial-based evidence for this overview. For over 20 years, Cochrane has produced systematic reviews of primary research in human health care and health policy. These are internationally recognised as the highest standard in evidence-based health care resources (Thomson, 2015). Furthermore, not only does Cochrane provide better methodological quality (Goldkuhle, Narayan, Weigl, Dahm, & Skoetz, 2018), its reviews are routinely updated with new data and best methods.

4.3.3 Taking data from the survey

From the work of Chapter III, the interventions most commonly used in Lebanese practice are now known (Dib et al., 2018) and these were used as the basis of the evidence sought in the Cochrane Library. Interventions not used in Lebanese practice were not sought.

4.3.4 Linking intervention to Cochrane evidence

Any intervention found to be used more than once in the Lebanon survey was highlighted, and a corresponding, directly relevant[2], Cochrane review sought in the Cochrane Library (September 2017). When no *directly* relevant review was identified then a review of some relevance was sought – albeit of *indirect* relevance[3]. Finally, should no review of direct or indirect relevance have been identified, this was noted in the results table (See Table 4.1: Overview of directly and indirectly relevant reviews (plus additional trials since initial publication).

4.3.5 Finding new evidence

An Achilles' heel of Cochrane reviews, however, is that many are not up to date (Kristiansen, 2008) and it is important for the development of this thesis to have *all* relevant evidence. By working with the Information Specialist of the Cochrane Schizophrenia Group (Farhad Shokraneh) new trials since the date of each review's publication were obtained. In addition,

[2] Direct relevance – where an intervention used in Lebanon (e.g. chlorpromazine) was the primary focus of a Cochrane review (e.g. Chlorpromazine in psychiatric emergency care) and where both intervention and control treatments are employed in practice in Beirut.
[3] Indirect relevance - where an intervention used in Lebanon's emergency practice was compared with another intervention *not* used in Lebanon.

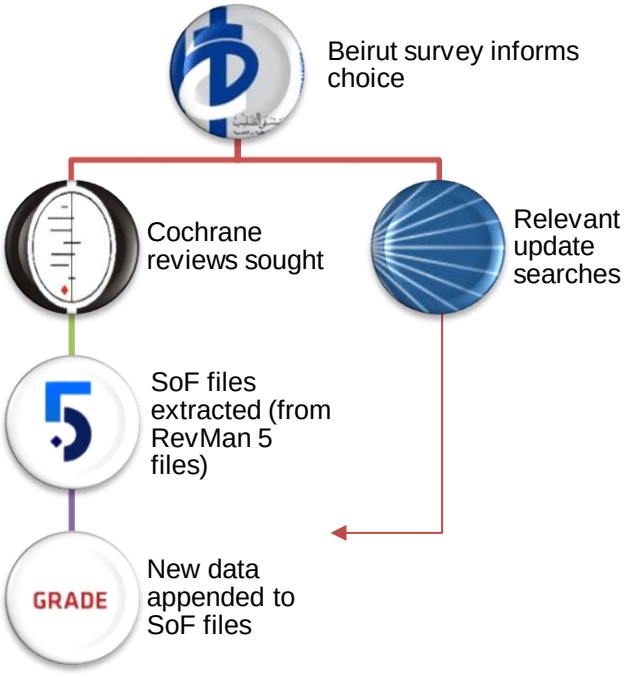
any trials relevant to the interventions used in Lebanon but for which there were no Cochrane review/s were also sought. Each of these individual trials were inspected to ensure they were indeed fully relevant. In addition, as of 6th September 2018, all trials relevant to Lebanese emergency psychiatry were systematically sought from clinicaltrials.gov. (Clinicaltrials.gov is a database of privately and publicly funded clinical studies conducted – or ongoing - from around the world provided by the US National Library of Medicine. It contains around 283,303 research studies from 50 states and 204 countries.).

4.3.6 Producing the overview of key outcomes/SoF tables

Each Cochrane review contains a table or tables that summarise the findings (Summary of Findings/SoF tables). These SoF tables use the GRADE system (Kavanagh, 2009) for presenting and quality-assessing limited numbers of key findings of any one review (Guyatt et al., 2011) and affords opportunity to produce overviews such as this chapter. Cochrane has tried to harmonise the outcomes chosen for each review when the reviews focus on similar topic areas – as in this case – the management of acute aggression thought due to serious mental illness.

Each of the SoF tables relevant to Lebanese emergency practice were extracted and appended with any new relevant trials identified by the update search. Where no Cochrane review existed and trials to a question relevant to Lebanese practice did, it had been hoped to review these to supplement and complete the series of SoF tables. Finally the SoF tables were amalgamated taking the outcome of primary importance to TREC-Lebanon (short term tranquil/asleep) or some near proxy if that was not available (Table 4.2: One primary outcome of key relevance to clinical practice in Lebanon from SoF table of reviews).

Figure 4.1: Methods schema



4.4 Results

Four directly relevant reviews to emergency practice in Lebanon were identified; three other interventions had no direct reviews while five (n>1) had partial relevance as shown in table 4.1 below. The relevant interventions indicate the treatment(s) used during an emergency episode and the frequency indicates how many times it was used as seen in the survey (Dib et al., 2018).

There were several directly relevant reviews. For example, straitjackets are used in the Lebanese psychiatric emergency setting and Cochrane Library does have a review solely relevant to 'seclusion and restraint' for people with serious mental illnesses (Sailas & Fenton, 2000). For example, promethazine (used alone) there was, however, only reviews of indirect relevance. One review investigating use of haloperidol *plus* promethazine in treating individuals at risk of aggression was available, and was added under the topic "promethazine" in the 'Indirect reviews' column (Table 4.1: Overview of directly and indirectly relevant reviews (plus additional trials since initial publication)).

Table 4.1: Overview of directly and indirectly relevant reviews (plus additional trials since initial publication)

		Relevant Interventions	Frequency (N>1)	Directly relevant reviews	Reference	Update trials (Total/ relevant)	Indirectly relevant reviews/titles	Reference	Update trials (Total/ relevant)
Non-Drug Intervention	Physical Restraint	**Straitjacket**	9	**Seclusion and restraint for people with serious mental Illnesses**	Sailas and Fenton (2000)	10/**4**	**De-escalation techniques for psychosis-induced aggression or agitation**	Du et al. (2017)	**0/0**
Drug	Antipsychotic drugs	**Chlorpromazine**	10	**Chlorpromazine for psychosis induced aggression or agitation**	Ahmed, Jones, and Adams (2010)	12/**1**			
		Promethazine	12	No Review		**0/0**	**Haloperidol plus promethazine for psychosis-induced aggression**	Huf et al. (2016)	6/**0**
	Combinations–including antipsychotic drugs	**Haloperidol + Promethazine**	8	**Haloperidol plus promethazine for psychosis-induced Aggression**	Huf et al. (2016)	55/**1**	**Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation)**	Ostinelli et al. (2017)	55/**9**
							Haloperidol for long-term aggression in psychosis	Khushu & Powney (2016)	
		Haloperidol + Promethazine + Chlorpromazine	18	No Review		**0/0**			0/**0**
		Zuclopenthixol + Promethazine	3	No Review		**0/0**	**Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses**	Jayakody et al. (2012)	9/**8**
	Benzodiazepines	**Diazepam**	16	**Benzodiazepines for psychosis-induced aggression or Agitation**	Zaman et al. (2017)	27/**3**			
		Lorazepam	**5**						

4.4.1 Non-pharmacological interventions

a. Seclusion and restraint (Appendix E, Table E1 Comparisons ①②③)

Straitjacket (restraint) was commonly used as a non-pharmacological intervention in Lebanese practice (n=9). The relevant Cochrane review by Sailas and Fenton (2000) has not been updated but 10 trials were attained from the fully up-to-date Cochrane Schizophrenia Register[4]. As the Cochrane review had not been updated for a long time a Summary of Findings table was absent. Of the ten trials sent only four were truly relevant. Data were extracted, inputted into RevMan, exported to the GRADE system by which a Summary of Findings table is created. In this way the evidence-gap was filled.

Comparison ① focused on seclusion versus restraint. Two randomised trials were included with a total number of 131 participants and a quality grade of 'moderate' for the key outcome. Comparison ② assessed restraint versus restraint – more specifically, restraint with bracers versus restraint with straitjacket. There was only one trial with 88 participants. The grade quality was rated as very low. Finally, comparison ③ focused on restraint versus body language comfort. It was

[4] https://schizophrenia.cochrane.org/register-trials

difficult to understand what the second intervention was, but it is felt to be some sort of talking restraint-avoidance technique. There was only one trial with 120 participants randomised. The quality of evidence was rated as 'low'.

b. De-escalation techniques

De-escalation techniques are categorised under indirectly relevant reviews and are part of the 'non-drug' intervention options. Only one review (n=1) conducted by Du et al. (2017) was found and the main results showed that of the 345 citations that were identified using the search strategies, only one reference to be potentially suitable for further inspection. However, after viewing the full text, it was excluded since it was not a randomised controlled trial.

4.4.2 Pharmacological interventions

a. Haloperidol vs. chlorpromazine (Appendix E, Comparison ④)

The original direct review found in Cochrane Library had only one relevant study. Another relevant study from 2010 (Ahmed et al., 2010) was added to the summary of findings table supplementing the total to now 161 participants (2 RCTs). The quality of evidence was rated 'low' as the initial review only had one study with 30 participants and the reviewers rated 'poor' based on small sample size, randomisation was not well

described, blindness unlikely and selective reporting was present. Though updated with another study, so with increasing sample size, quality is still poor, and it remains unclear if chlorpromazine reduces aggression anymore – or less - than haloperidol.

b. Haloperidol + promethazine vs. haloperidol (Appendix E, Comparison ⑤)

The initial summary of findings table from the review found only one study (n=316 participants). One additional trial relevant to Lebanon was added to the SoF table pushing up the total number of participants to 416. Overall, the review authors concluded that haloperidol plus promethazine was clearly more effective in reducing aggression compared with just haloperidol – with a rating of 'high' quality of evidence. There seems no reason to change the rating or the conclusion in the light of the additional evidence. Haloperidol plus promethazine is the second most prevalent option used in combination in Lebanese psychiatric emergencies.

c. Zuclopenthixol + promethazine (Appendix E, Comparison ⑩)

Zuclopenthixol plus promethazine was used in Lebanese psychiatric practice but there were no reviews reporting this combination. Instead, there were some data of partial

relevance on zuclopenthixol being used on its own when treating aggressive psychiatric patients. Within this review there were 'low quality' data – with major problems of imprecision as the one included trial totalled only 40 people. Results were equivocal. There was also one indirect relevant review focusing on the use of zuclopenthixol only with 8 out 9 RCTs relevant to the review.

d. Promethazine vs. anything (Appendix E, Comparison ⑪)

Promethazine on its own has never been tested for treating aggression within a randomised trial. In Lebanon, however, promethazine, on its own, was used 12 times – making it one of the top three interventions used in Beirut. A review of indirect relevance focused on haloperidol *plus* promethazine for psychotic induced aggression (see above). An indirect review looking at haloperidol plus promethazine was included but out of 6 trials, none were relevant.

e. Haloperidol + promethazine + chlorpromazine (Appendix E, Comparison ⑫)

The main combination used in Lebanese psychiatric practice for treating individuals at risk of an aggressive episode was the HPC combination of medications – this was used most

frequently of any drug treatments (18 times; 46 % of total). There are no randomised trials involving this combination.

f. Benzodiazepines for psychosis induced aggression or agitation (Appendix E, Comparison ⑥⑦⑧⑨)

The Cochrane benzodiazepine review contained multiple interventions, and multiple comparisons with relevance to Lebanese practice (Dib et al., 2018). The first relevant comparison was benzodiazepine versus placebo (Table 4.2, Comparison ⑥). There was only one study (102 participants) and quality of evidence was rated 'very low' – but there was no clear difference between the benzodiazepine and use of placebo.

The second comparison focused on benzodiazepines versus antipsychotics (Table 4.2, Comparison ⑦). The summary of findings table included data from 8 studies (total of 434 participants). The reviewers rated the quality of evidence as 'low' citing risk of bias and imprecision. The best estimate of effect included both 'no effect' and appreciable benefit/harm.

The third comparison included data on benzodiazepines (in reality lorazepam) versus antihistamines (promethazine) plus antipsychotics (haloperidol) (Table 4.2, Comparison ⑧). The summary of findings table listed only one study (200 participants). The reviewers rated the quality as 'low', but the

primary outcome did just favour the haloperidol plus promethazine group.

The fourth comparison was antihistamines plus antipsychotics (promethazine + haloperidol) vs. benzodiazepines plus antipsychotics (lorazepam + haloperidol) (Table 4.2, Combination ⑨). The review's summary of findings table had only one study with a total of 60 participants (rated as 'very low' quality). There was no clear difference between the treatment groups.

Table 4.2: One primary outcome of key relevance to clinical practice in Lebanon from SoF table of reviews

COMPARISON	**TREATMENT 1**	**TREATMENT 2**			
Outcome closest to binary – tranquil/asleep	Illustrative comparative risks* (95% CI) Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)
①	**Restraint**	**Seclusion**			
Became tranquil or asleep/ episode over	**576 per 1000 (420 to 780)**	**600 per 1000**	RR 0.96 (0.7 to 1.3)	131 (2 studies)	⊕⊕⊕⊖ moderate
②	**Restraint (Bracer)**	**Restraint (Straitjacket)**			
Global state: Not improved - impulsiveness	**101 per 1000** (30 to 330)	**150 per 1000**	RR 0.67 (0.2 to 2.2)	88 (1 study)	⊕⊖⊖⊖ very low
③	**Restraint**	**Language Body Comfort**			
Became tranquil or asleep/ episode over: (not 'angry')	**549 per 1000** (441 to 675)	**900 per 1000**	RR 0.61 (0.49 to 0.75)	120 (1 study)	⊕⊕⊖⊖ low
④	**Haloperidol**	**Chlorpromazine**			See note 1
Global outcome**: Number of additional injections - 2-4 injections	667 per 1000	600 per 1000 (347 to 1000)	RR 0.9 (0.52 to 1.55)	161 (2 RCTs)	⊕⊖⊖⊖ very low
⑤	**Haloperidol**	**Haloperidol +promethazine**			See note 2
Tranquil or asleep[1]: Not tranquil or asleep Follow up: 30 minutes	500 per 1000	325 per 1000 (245 to 435)	RR 0.65 (0.49 to 0.87)	416 (2 RCTs)	⊕⊕⊕⊕ high
⑥	**Placebo**	**Benzodiazepines**			
Tranquilisation or asleep- sedation Follow-up: 24 hours	59 per 1000[1]	98 per 1000 (25 to 389)	RR 1.67 (0.42 to 6.61)	102 (1 RCT)	⊕⊖⊖⊖ very low
⑦	**Haloperidol**	**Benzodiazepines**			See note 3
Tranquilisation or asleep- sedation Follow-up: mean 16 hours	100 per 1000	113 per 1000 (83 to 154)	RR 1.13 (0.83 to 1.54)	434 (8 studies)	⊕⊕⊖⊖ low
⑧	**Haloperidol + promethazine**	**Lorazepam**			
Tranquilisation or asleep- sedation Follow-up: 2 weeks	970 per 1000[1]	883 per 1000 (815 to 951)	RR 0.91 (0.84 to 0.98)	200 (1 RCT)	⊕⊕⊖⊖ low
⑨	**Haloperidol + promethazine**	**Lorazepam + antipsychotics**			
Tranquilisation or asleep- sedation Follow-up: 12 hours	33 per 1000[5]	400 per 1000 (55 to 1000)	RR 12 (1.66 to 86.59)	60 (1 RCT)	⊕⊖⊖⊖ very low
⑩	**Standard drug care**	**Zuclopenthixol acetate**			
Not sedated Follow-up: 4 hours	900 per 1000	666 per 1000 (486 to 900)	RR 0.74 (0.54 to 1)	40 (1 RCT)	⊕⊕⊖⊖ low
⑪	**Promethazine**	**Anything**			
Any outcome relevant to acute aggression or agitation	No relevant trials.				
⑫	**Haloperidol + promethazine + chlorpromazine**	**Anything**			
Any outcome relevant to acute aggression or agitation	No relevant trials.				

1: 1 study **(Ahmed et al., 2010)** added to SoF table from 2010 review
2: 1 study found (Abolhassanzadeh, Shafiee-Kandjani, Shafiei, & Beiraghi, 2016) (n=100) and added into review's SoF
3: One trial found relevant to Lebanon (Srinath 2010) with sample size smaller than review n=6

4.5 Discussion

These novel review techniques have summarised the best evidence of treatments relevant to aggression in Lebanon in a way that is time efficient. Updating has been targeted on comparisons and outcomes of importance in Lebanon and, although more effort would have to be made to fully update each Cochrane review, it would seem unlikely that significant bias has been introduced to this chapter by use of this swift update technique.

4.6 Conclusions

There is no randomised trial of the most common drug intervention used in Lebanon (the haloperidol, promethazine, chlorpromazine combination). This does not mean that this triple combination does not work. The use of these three drugs together has been tested in clinical life for years and, if it were ineffectual this would have been obvious. However, in the psychiatric emergency when a person is violent and treatments are going to be used without consent, there is an imperative to use the safest least restrictive and intrusive option (Nadkarni et al., 2015). If lower doses are as safe as the higher ones, the lower should be employed. If fewer drugs are as effective as more, then the former should be favoured. The *comparative* effectiveness of the triple combination is

likely to involve subtle differences to other treatment regimens and can really only be confidently highlighted by fair testing within a randomised trial (Evans, Thornton, Chalmers, & Glasziou, 2011). The following chapter describes the design of such a study.

Overall, the quality of evidence relevant to the treatments in everyday use in Lebanon is variable. Quality ratings of the key outcomes of interest range from non-existent through 'very low' (the commonest grading) to 'high' (once) (Table 4.2). The key issue is that the highest quality evidence is for an intervention that is available and acceptable in Lebanon (haloperidol + promethazine) and that evidence (from trials) for one of the commonest used drug interventions (the haloperidol, promethazine, chlorpromazine combination) does not exist. This discrepancy helps the argument for testing this particular combination within two arms of a randomised trial. The next chapter describes the collaborative, pragmatic design of such a trial.

5. Chapter V- Protocol of a pragmatic randomised controlled trial: intramuscular haloperidol, promethazine and chlorpromazine (HPC) versus intramuscular haloperidol and promethazine (HP) for people who are acutely aggressive and for whom medication is indicated, in the Lebanese psychiatric setting.

5.1 Overview

Chapter IV was a systematic overview of relevant trials and it concluded with showing the emergency treatment (HPC) used in Lebanon (See Chapter III) is unique to Lebanese medical practice. This chapter will focus on the trial protocol building on chapter III (treatment in Lebanese practice) and chapter IV (Systematic overview of relevant trials pertaining to rapid tranquilisation).

Between Chapter IV and Chapter V, much has happened behind the scenes. In order to commence the coming trial, the associates of the Psychiatric Hospital of the Cross and the University of Nottingham Ethics Board had to agree on the trial design. This meant the head researcher (Myself) had to constantly travel back and forth several times until an agreement between both institutions were reached. Being physically present served to build relationships between the

clinicians, nurses and all those who would be involved in the TREC-Lebanon trial. I was able to personally meet the residents who would be part of the trial and answer any questions pertaining to the trial itself. Some residents refused to participate in the trial for personal reasons (i.e. additional workload) while others agreed to participate as they saw the importance of conducting such a trial. As the trial had no additional funding, I could only promise the chance of having their names on the published trial manuscript.

The decision on trial design was accepted by the head clinicians of the Lebanese hospital of the cross. However, the University of Nottingham's School of Ethics were unsatisfied and advised me to submit the trial's ethics application to the University's main body of ethics who responded that the trial is better situated for the school's divisional ethics. This went back and forth for a period of seven months before a final decision was made with the school's divisional ethics stating that no ethics is required from the University's part as it is a Lebanese trial but stated all data pertaining to patients should be anonymised if data analysis was conducted on UK soil. For more information on ethics, see Chapter VII. In order to not waste time waiting for ethics to give approval, I designed and wrote this chapter in publication format as I had to register and publish the trial protocol before the trial commenced.

5.1.2 Aims

Chapter V is a research protocol of the clinical trial that is to be conducted in the Lebanese psychiatry setting. It describes how the clinical trial will be conducted (I.e. objectives, statistical considerations, design, methodology and organisation) and ensures the ethical integrity of the trial subjects and data acquisition have been considered. Moreover, the protocol (now registered and published) serves as an indicator that the trialists will conduct the trial in accordance to what is presented in the trial protocol. Should the trial stray in any of its aims (i.e. result objectives), the trialist is obliged to explain why changes were implemented.

5.2 Introduction

Aggressive and violence behaviour is a common behaviour seen in emergency psychiatric presentations with a prevalence of 3-10% (Tardiff & Koenigsberg, 1985). This aggression is due to a range of psychiatric disorders such as schizophrenia, bipolar disorder, substance use, and personality disorders as well as organic problems such as dementia although they are less frequent with the latter (Kaplan & Sadock, 1998). Guidelines recommend that individuals who are at risk for an aggressive episode to be 'verbally tranquilised' in order for the attending physician to accurately and safely perform a

diagnostic history and physical examination (The expert consensus guideline series, 1999). Since patients who are at risk for an aggressive episode make this process difficult and potentially impossible, doctors and nurses face a dilemma and are required to work with limited evidence. Since the psychiatric team has a responsibility of ensuring the safety of everyone, rapid and safe tranquilisation becomes unavoidable. Medication and physical restraints are the available options when planning to calm and tranquilise an agitated patient. Medication can be given orally, intravenously (IV) or intramuscularly (IM). Oral and IV medications are usually not possible when the patient is lashing out aggressively (Yildiz, Sachs, & Turgay, 2003). Depending on where in the world the management is happening, physical restraints may include straitjackets (Colaizzi, 2016), use of seclusion rooms (Crespi, 1990) or medical restraints binding the patient safely to a bed using two or four points (Fisher, 1994; Saks, 1986). Physical restraining by staff is commonly employed.

All options have advantages and disadvantages. For example, IV medication may work faster when tranquilising an agitated patient but may also lead to cardiac and respiratory problems – not to mention extreme difficulties implementing IV needles with an aggressive patient (Atakan & Davies, 1997). IM medications are easier to administer making them more

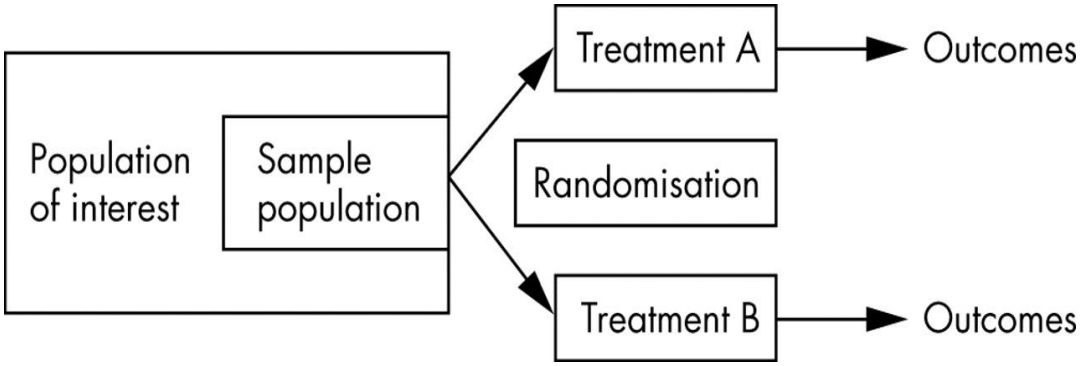
efficient in terms of implementation. However, the time to onset of calming or sedation is longer and unpredictable compared to IV (Kaplan & Sadock, 1998). Physical restraints have the advantage of preventing patients from physically assaulting staff as well as causing self-injury. They also have the advantage of being more efficient when used in combination of drugs being delivered via IV or IM (Currier & Trenton, 2002). However, the disadvantages of restraints include out of date practice (depending on country) and time taken for patient to achieve a state of calm is profound when compared to pharmacological interventions (Miles & Irvine, 1992). It is imperative to find an evidence-base for a management scheme that is humane, socially acceptable and suited to tranquilise/calm patients who are at risk of aggression safely and rapidly. This will help ensure the safety of both patients and the workers involved. TREC-Lebanon is a randomised, controlled, pragmatic and open study. Primary measure of outcome is tranquilisation at 20 minutes but effects on other measures of morbidity will also be assessed. TREC-Lebanon will involve the collaboration of many health care professionals – clinicians and psychiatric nurses in wards whereby the trial is taking place. Because the design of the trial does not substantially complicate clinical management, and in several aspects simplifies it, the study has the potential

to be large and to evaluate treatments used in everyday practice.

5.2.1 What is a randomised controlled trial?

A randomised controlled trial is a type of study in which a number of similar people are randomly assigned to two (or more) groups in order to test a specific drug, treatment or intervention The experimental group receives the intervention being studied while the control group receives a placebo, no intervention or an alternate intervention. Outcomes are measured at specific times and the differences are examined statistically. This method is used to reduce bias (National Institute of Clinical Excellence, 2005). Figure 5.1 shown below is a classic example of the basic structure of a randomised controlled trial (Akobeng, 2005).

Figure 5.1: The basic structure of a randomised controlled trial

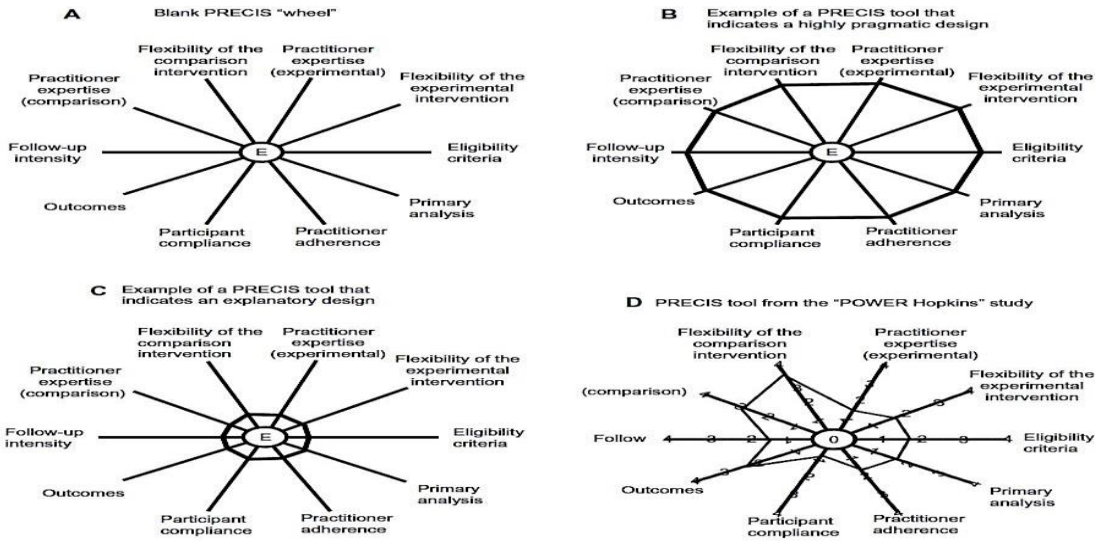


5.2.2 What is a pragmatic randomised trial?

The term explanatory is used to describe trials that aim to evaluate the efficacy of an intervention in a well-defined and

controlled setting, Pragmatic or 'real-world', however, is used for trials designed to test the efficacy of the intervention in routine clinical practice (Patsopoulos, 2011). For example, a trial intended to inform a research decision regarding the benefit of a new drug is more likely to be explanatory reflecting ideal conditions while those for a later trial of the same drug intended to inform practical decisions by clinicians are more likely to be pragmatic as they reflect the usual conditions (Thorpe et al., 2009). The PRECIS instrument has been developed to guide trial design at the planning stage but also serves in other applications such as peer reviews attained in study reports (Winter & Colditz, 2014).

Figure 5.2: PRECIS tool



5.2.3

Rapid tranquillisation

Rapid tranquillisation (RT) is not considered a 'treatment' for a persons' mental health condition, but a short-term

management technique for severely agitated and/ or aggressive behaviour in people experiencing psychotic distress. Due to its restrictive nature, RT should only be used as last resort when all other attempts to calm a situation via prevention (being environmentally aware and ensuring that adequate numbers of staff are present on ward) and de-escalation (talking to and verbally trying to calm the person) has failed. These interventions should always be used in a way that respects human rights and should never be used to manage patients as a substitute for adequate staffing (Department of Health, 2015).

5.2.4 Lebanese National Guidelines

There are no Lebanese national guidelines pertaining to rapid tranquilization. As illustrated by Chapter IV, evidence from trials regarding the emergency intervention favoured in Lebanon (Chapter III – HPC) does not exist, although there is a good evidence base for the HP combination that is also used in Beirut. This affords opportunity to compare these two management plans, in real world circumstances, within a pragmatic randomised trial. This will be first of its kind comparing these two approaches, but also the first of its kind in psychiatry in Lebanon.

5.2.5 TREC

TREC-Lebanon derived its name from the first Brazilian TREC-Rio study. TREC, in Portuguese, was an abbreviation for 'Tranquilização Rápida-Ensaio Clínico' [Rapid Tranquilisation Clinical Trial]. TREC-Lebanon, similar to TREC-Rio and TREC-India, will be investigating rapid tranquilisation within a clinical trial for treatment of agitated people in emergency psychiatric wards - in this case in Deir Salib – Lebanon's largest and only public psychiatric hospital.

5.3 Methods

5.3.1 Eligibility

TREC-Lebanon is a pragmatic trial with wide, easily applied eligibility criteria that have been drawn up by the researcher (JD) working with partners in the Psychiatric Hospital of the Cross, Beirut.

a. Inclusion criteria

Patient will be eligible if (1) requiring emergency acute intramuscular sedation because of disturbed and dangerous behaviour and (2) if the clinician is uncertain of the benefits between haloperidol plus promethazine vs. haloperidol plus promethazine plus chlorpromazine.

- Gender – both male and female
- Age (18-64)

b. Exclusion criteria

- If the clinician KNOWS one treatment has benefit over another for a particular person
- If the clinician is aware of a contra-indication of one of the treatments
- If there is an Advanced Directive expressing a wish for one or other, or another treatment in the emergency setting

- If the clinician does not want to undertake for both personal and professional reasons
- If the participant is known to be allergic to one or more of the interventions
- Already randomized
- Already sedated
- Accompanying person (Friend/Family/Police Officer) refuses patient trial entry.

Table 5.1: TREC- Lebanon plan

Eligible if	• *Patient is needing acute intramuscular sedation because of disturbed and dangerous behaviour* • *Clinician is uncertain about the benefits and risks of haloperidol plus promethazine versus HPC*
Exclude if	• The Clinician believes that one treatment represents an additional risk for the patient

Trial Entry	• Treatment is allocated using opening of consecutive TREC envelopes stored in the emergency drug cupboard. The envelope contains:
	  • The treatment paper slip indicating intervention to use
	  • TREC forms to be filled out by the attending doctor/resident
	  • TREC stickers for the patient's notes

Treatment	• Either:
	  • Haloperidol (2x5mg ampules) + promethazine (1x50mg ampules)
	  Or:
	  • HPC (Haloperidol 5 mg, Promethazine 50 mg and Chlorpromazine 100 mg ampule)
	• One or other indicated on paper slip in the TREC envelopes
	• All doses are at the discretion of the doctor

Follow up	• All people for whom an envelope is opened will be followed up by the TREC study co-ordinators • Data will be extracted from the notes on clinical state, hospital status, sedations, use of additional medications, and adverse reactions

5.3.2 Interventions

Placebo controlled studies in this area are difficult to justify on ethical grounds (see section on ethics in chapter 7.6.1 Ethics) although the UK National guideline (National Institute of Clinical Excellence, 2005) does use evidence from such studies

(See here). TREC-Lebanon, however, will evaluate the existing care in the health services of Lebanon (Chapter VI) and this care involves the use of medication that is considered – and most likely is - both safe and effective. Currently, this protocol includes a comparison of an intramuscular haloperidol-promethazine mix (HP) with an intramuscular haloperidol-promethazine-chlorpromazine mix (HPC).

The triple mix (HPC) is an obvious choice for TREC-Lebanon. It is perceived as effective, safe, and with adverse effects that are readily recognised by both medical and nursing staff in their routine care (See Chapter III). It is easy to administer by intra-muscular injection but has never been evaluated within a randomised control trial. As seen in Chapter III, the HP mix is also used in Beirut, albeit less frequently. Haloperidol, promethazine and chlorpromazine are on the WHO's Model List of Essential Drugs (See here) (World Health Organization, 2015).

a. Chlorpromazine

Chlorpromazine is one of the three listed drugs for treating psychotic disorders in the World Health Organization's Essential Drug List (World Health Organization, 2013) (See here). It is used across the globe for the 1% of people who suffer from this illness (de Haan & Liu, 2009). Chlorpromazine

has a number of adverse effects, including a range of movement disorders (extrapyramidal symptoms) and anticholinergic and antihistaminic effects (Abidi & Bhaskara, 2003). Chlorpromazine is known to be the most epileptogenic of the conventional antipsychotics causing seizures ranging from 1-4% depending on dosages (Hedges, Jeppson, & Whitehead, 2003).

b. Haloperidol

Haloperidol is an effective antipsychotic also listed in the World Health Organization's Essential Drug List (World Health Organization, 2013). A key adverse effect caused by haloperidol is acute dystonias which are involuntary contractions of muscles all over the body such as the neck, face, pelvis, extremities, etc. and occur in 40% of all patients under haloperidol treatment (Kurz, Hummer, Oberbauer, & Fleischhacker, 1995). They are not life threatening but can be distressing and frightening to the patient. Acute dystonias are successfully and swiftly treated with use of anticholinergic medication such as promethazine or procyclidine (Adams, Bergman, Irving, & Lawrie, 2013). However, these events are highly unpleasant and must further erode trust in the services.

c. Promethazine

Promethazine hydrochloride is a first-generation H1 receptor antagonist, antihistamine, and antiemetic medication that can also have strong sedative effects ranging from mild to heavy and is used in relieving extrapyramidal symptoms caused by antipsychotic medications (Cantisani et al., 2013). Anticholinergic manifestations such as dry mouth, mydriasis, and blurred vision are usually present. Overdosage may also present with various cardiorespiratory symptoms such as respiratory depression, tachycardia, hypertension or hypotension, and extrasystoles (Lazarou, Pomeranz, & Corey, 1998).

d. The combinations

It is well known that combining drugs can change - increase or decrease - the incidence of the known adverse effects (Lemmens, Brecher, & van Raelen, 1999) or result in novel effects unheard of with each drug on its own (Rummel-Kluge et al., 2010). The HP combination is, however, widely used and trusted. The addition of the promethazine to haloperidol may increase sedation, but decrease the acute dystonia so often seen with haloperidol alone. The latter was so common in the haloperidol alone arm of the TREC-Rio-II trial (Haloperidol vs. haloperidol + promethazine) and rare in the

second arm of that study that the trial was halted early by the Trial Steering Group (Huf, Coutinho, & Adams, 2007). It was felt that the combination treatment had considerable advantages over the haloperidol alone arm and that it was unethical to continue randomising to such a toxic treatment. (This latter treatment continues to be commonly employed within UK practice and can be seen in the 2017-2018 Prescribing Observatory For Mental Health: Available to download here) (Prescribing Observatory for Mental Health (POMH-UK), 2018).

The combination of haloperidol, promethazine and chlorpromazine (HPC) seems to be less commonly used than the combination of haloperidol and promethazine. However, HPC is still used in everyday practice at least Brazil and Lebanon (Dib et al., 2018; Huf, Coutinho, & Adams, 2002). Whether the further addition of another drug (chlorpromazine) is a benefit or causes difficulties will, partly, be illustrated by the results of this study but no literature has been found to suggest that there are novel or even extreme adverse effects of this triple combination. Chapter III's survey of Lebanon has shown that this intervention has been commonly used in psychiatric practice – probably for many years - with success in attaining rapid tranquilisation as well as causing very low incidence of adverse effects.

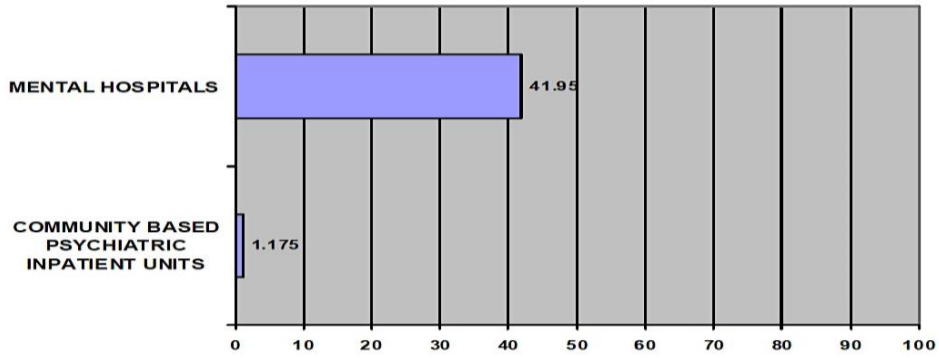
5.3.3 Setting

The prevalence of serious mental illness across the world is 1-2%. 80% of people live in low- or middle-income countries where typical antipsychotics such as haloperidol and chlorpromazine and/or benzodiazepines are readily available. Lebanon ranks as a low to middle income country (El Laithy, Abu-Ismail, & Hamdan, 2008). And, indeed, the 'typical' antipsychotics plus benzodiazepines are used (Chapter III).

There are three mental hospitals and five psychiatric units within general hospitals in Lebanon. There is a total of 43 psychiatric beds per 10,000 population (figure includes both psychiatric beds in general hospitals and mental hospitals). Two psychiatrists per 100,000 populations can be found in the general Lebanese population. Lebanon depends mainly on the private sector for the provision of the health services. The Ministry of Health has contracts with several private sector providers so patients can receive 'free' treatment. There are no disability benefits for persons with mental disorders and no disability funding for mental health (Berger, 2007). There are also no existing data on people who are treated in mental health hospitals, general hospital and community based psychiatric units. At best, by combining data from below on Lebanon's economic social status and data from the WHO-AIMS report on Mental Health in Lebanon (World Health

Organization, 2010), it can be assumed that since the majority of patients are treated in mental hospitals compared to community based psychiatric inpatient units (See Figure 5.3) and that the majority of the population require services from the Ministry of Health as they cannot afford private insurance, the majority of people seeking treatment for mental health would choose public psychiatric hospitals over private (Berger, 2007).

Figure 5.3: Patients treated in mental health facilities (rate per 100.000 population)



5.3.4 Size and statistical considerations

Two main factors determine the number of people who should be recruited in a randomized trial in order for the trial to provide clear answers. They are the frequency of the investigated event and the size of the effect of treatment. It is important to avoid results that are erroneous. The probability of producing so called 'false-positive' results (Type I error – a) and 'false negative' findings (Type II error – B) is minimised by having adequate sample size. The aim of TREC-Lebanon is

to investigate whether people do 'better' if they get HPC or HP and 'better' – the primary outcome - is the proportion of patients' calm/tranquil at 20 minutes.

In such a stressful situation, even a small advantage for an intervention could represent a worthwhile benefit and so, TREC-Lebanon has been planned so that even a 15% difference in the proportion of tranquilised patients within the 20 minutes could be detected. Realistically, and calculated from work in Chapter III and the time constraints of this PhD, TREC-Lebanon expects to involve a minimum of 90 patients across at least in a 3-month period.

Table 5.2: Sample size needed to detect an absolute difference

HP (% tranquilised)	HPC (% tranquilised)	*N*
5	20	152
10	25	200
15	30	242
20	35	276
25	40	304
30	45	326
35	50	340

As seen above sample size needed to detect an absolute difference of 15% in the proportion of tranquilised patients with alpha being 5% is greater than what TREC-Lebanon is projected to accrue. Therefore, TREC-Lebanon may well be underpowered to detect real effects and will not hold the same strength as TREC-Rio and TREC-India. However, the difference

between the two management strategies under test could be greater than 15%. Also, TREC-Lebanon is the first of its kind, it will serve as a vanguard for such studies in the Middle East and properly test feasibility, as well as being a pilot for trials to come.

5.3.5 Ethical and legal considerations

The Helsinki Declaration (World Medical Association, 2013), the European Directive on Clinical Trials (European Parliament, 2002) and the Nuffield Council documents on bioethics (Nuffield Council, 2000) state that trials in non-consenting patients are permitted on two conditions: i. no other context exists in which to answer the question; and ii. All trial participants get clear therapeutic benefit from whichever arm they are randomised to.

The mental health system benefits from different acts and legislations in different areas of mental health (Berger, 2007), namely:

- Lebanese Act no. 72-9/9/1984 Welfare Act and Protection and Treatment of Mentally Ill Patients.
- Lebanese Act no. 673-16/3/1998 Narcotic Drugs and Psychotropic Substances and Precursors.
- Lebanese Act no. 220-29/5/2000 Rights of Mentally Handicapped in Lebanon.

- Lebanese Act no 574-11/2/2004 Patients' Rights and Informed Consent.

Patients who are at risk of aggression in a situation of psychiatric emergency are not able to give consent for their participation in a study (see

Appendix G). Drugs are usually given against the will of the patient. So, in the same way that doctors are responsible for the choice of a treatment in routine care, they take responsibility for the recruitment of a patient into the study as well as seeking consent. However, TREC-Lebanon will not involve administering an inactive compound to those who clearly need sedation/tranquillisation. Both treatments can calm the patient and there is no 'experimental' intervention. What is still uncertain is the speed for the onset of action, the duration of the effects and the different kinds of adverse reactions. TREC-Lebanon will answer clinical questions to help the care of these people be more informed. TREC-Lebanon will also produce widely applicable findings, so that the treatment of people beyond Lebanon should also be safer.

A patient/carer information leaflet about TREC-Lebanon is available for all for whom a TREC-Lebanon envelope is opened. Carers will always be free to decide that their relative should not be entered. Not being involved in TREC-Lebanon will not affect the person's standard of care. An information sheet is

provided detailing the aim and purpose of the study (See Appendix F).

5.3.6 Randomisation

Randomisation allows the distribution of the treatments in a way that is not a function of a clinical decision, but of pure chance. Clive Adams will undertake randomisation in the United Kingdom. Microsoft Excel 'RAND' function will be used to choose even numbered block sizes less than ten. Again, using this function, the order of use of these block sizes will be randomised. Which drug regimen was represented by which number within the block was then selected, again at random. Tables of TREC-Envelopes numbered by contents will be constructed and will be supplied to a Lebanese colleague (Souheil Hallit). The tables will list the contents of the envelopes in groups of ten, not disclosing the block sizes used. The Lebanese colleague, always working independently of the TREC-Lebanon team, will ensure that the correct labels are in the TREC-envelopes before they are sealed. Concealment of allocation will be ensured by not disclosing the randomly varied block sizes to the colleagues packing the envelopes, the supply of tables to those colleagues that gives no suggestion that blocks are even being employed, the independence of those filling the envelopes from the other researchers or the

clinicians, and the identical nature of the sealed, fully opaque envelopes.

These easy-to-use envelopes will be paper based, identical and consecutively numbered. The final check to ensure that nothing has gone wrong with the randomisation will be by the principal investigator (JD) filling in a form for each block of ten opened envelopes.

5.3.7 TREC-Lebanon

Because the TREC-Lebanon study evaluates care in the emergency situation, it is imperative that the doctors and nurses know which intervention is being given. The study is blind only up until the time that the TREC-Lebanon trial envelope is opened. Therefore, it is crucial that the evaluation of the severity of a person's disturbance and the first impression on the possible cause for the disturbed behaviour are recorded *before* the envelope is opened. Once the envelope is opened, doctors and nurses will have knowledge of the drug to be used. It is perfectly feasible that the knowledge that one drug has been given will influence the care beyond the actual effects of the medication. Keeping the study open is not only practical in the emergency situation, but also desirable as the evaluation of care being undertaken is as near real-world circumstances as is possible.

5.3.8 Protocol registration

The objective of registering trial protocols is to establish a comprehensive register that would make all protocol of trials publicly available (Dickersin & Rennie, 2003).

Reference number supplied by the chairman of the committee of The Psychiatric Hospital of the Cross Lebanon: HPC 001/2018.

Reference number supplied by the ethics board of the University of Nottingham: 271.

5.4 Procedures

All trial materials, and guidelines for their use, are to be provided in the TREC-Lebanon folder supplied by the co-ordinating centre. What follows is a brief summary of all of trial procedures.

5.4.1 Fitting into everyday practice

The TREC-Lebanon trial is designed to not interfere with routine care. The process of randomisation is very similar to the normal procedure at the beginning of treatment and the eligibility criteria are simple. A paper slip indicating what intervention to use will be packed within the envelope. Data collection will be limited to the minimum necessary and will involve little more than extraction of routine information by a

person designated to spend time on the TREC-Lebanon trial. It is not envisaged that busy doctors and nurses will be spending time filling out complicated forms.

5.4.2 In the community

Chapter III survey showed there are times when patients are brought in after having been given a sedative to calm down by their parents, friends or law officials. In this situation, as far as the clinician is concerned, he or she must still decide if the patient should be randomised if the patient is still exhibiting an agitated episode.

5.4.3 Arrival at hospital

Most people arrive at the hospital's administrative centre are registered as a patient, and then transferred into their ward. If patients are presenting with violent conduct that could potentially harm people in their vicinity, they are taken immediately to the designated ward while those who brought them to the hospital (Family, friends, police officers, etc.) fill out paperwork and present their documents to the hospital's administration. Patients that display an agitated episode requiring rapid tranquilisation are usually calm while waiting in the ward. Upon being told they cannot leave until they are feeling better, they may then display an agitation or aggression.

5.4.4 Triage to randomisation

a. Eligibility and randomisation by envelope.

Carers accompanying the disturbed person should have an opportunity to see the information leaflet (Appendix F) before randomisation.

Anonymised information on participants who are not randomised / registered will include:

- Age,
- Gender,
- Ethnicity (if applicable),

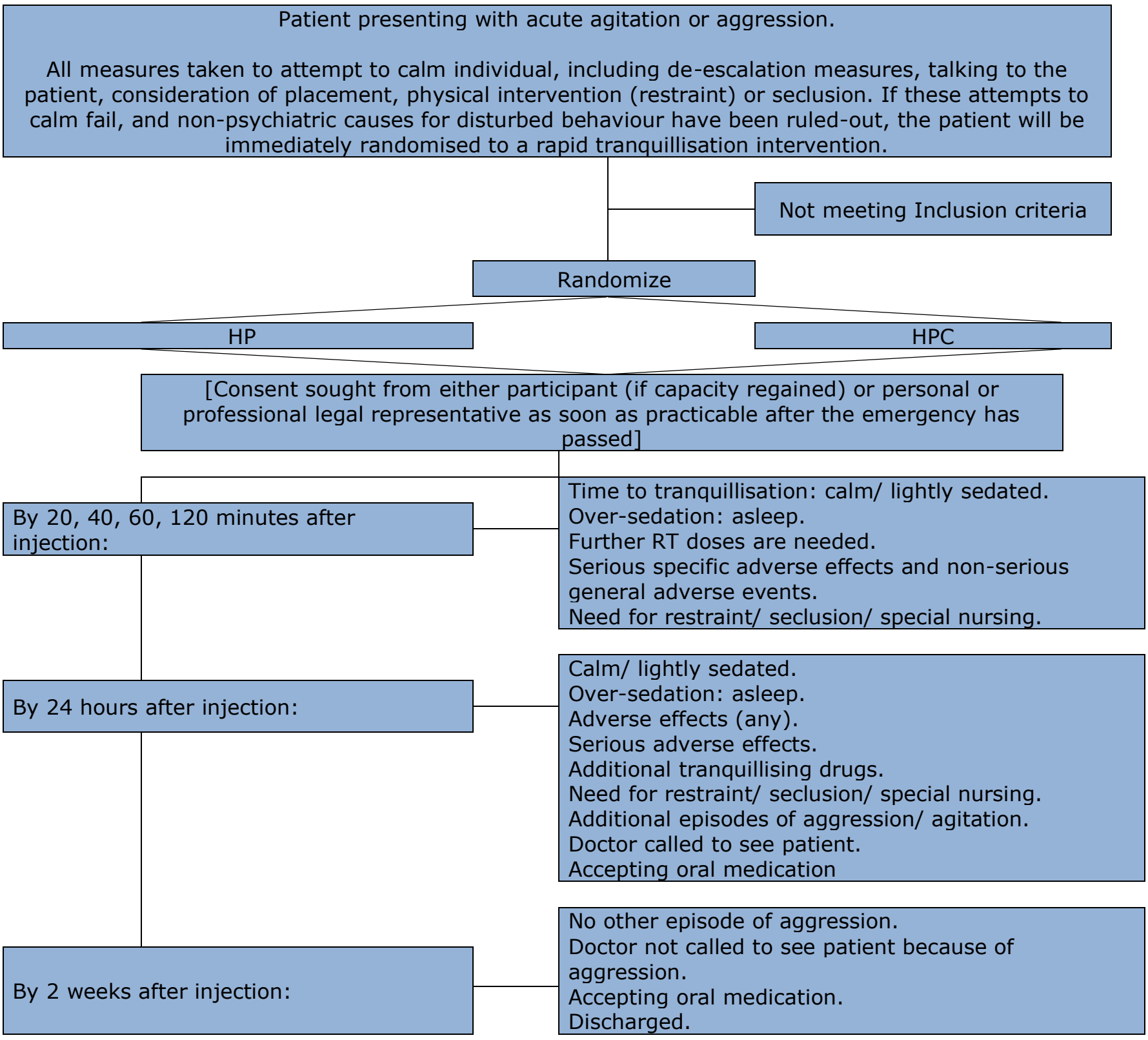
The reason not eligible for trial participation, or if they are eligible but declined.

Randomisation proceeds using a local pack system. Identical sealed treatment envelopes are provided.

As soon as the person enters the study, the clinician completes the trial entry form *on the top of the next consecutive envelope* (See Appendix H). This must be completed *before* the treatment envelope is opened. It records brief baseline details about the person and the number of the treatment envelope. The treatment envelopes *must* be used in order in which they are removed, the lowest number first. Once the trial entry form has been completed the person is in

the trial, even if the doctor changes his/her management and the treatment envelope is not opened.

Table 5.3: Follow up enrolment



5.4.5 Participant Eligibility Criteria

The eligibility criteria should be clear (See Eligibility above in Methods section).

5.4.6 Trial envelopes

As soon as the person has been found to be eligible, the next consecutive envelope is opened and a paper slip indicating what intervention to use is displayed. Each envelope contains:

Paper slip indicating the use of haloperidol + promethazine (HP)

1 × TREC-Lebanon follow-up form (See Appendix F)

2 × TREC-Lebanon stickers for the drug prescription form and medical notes

Or

Paper slip indicating the use of haloperidol + promethazine + chlorpromazine (HPC)

1 × TREC-Lebanon follow-up forms (See Appendix F)

2 × TREC-Lebanon stickers for the drug prescription form and medical notes

All doses used are at the discretion of the attending clinician. If the contents of a trial envelope are destroyed, or unfit for use, the person should *not* be randomised a second time and the equivalent material should be obtained from the research director (SH) if appropriate.

In the event of continuing aggression despite the TREC-Lebanon medication, on-going emergency management would be up to the discretion of the clinicians. Another envelope *is not* opened and the doctor is free to use any standard interventions.

5.4.7 Outcome and follow-up

It is crucial that follow-up is complete and accurate for everyone entered into the study. As a pragmatic study, causing minimal interference with routine care, TREC will not employ any rating scale outcomes. It is likely that completion of scales would be inaccurate, and incomplete, validity and reliability would be in question, and clinical utility problematic. The main outcome of TREC-Lebanon is tranquillisation by 20 minutes. This primary outcome was requested by the nursing and medical staff of the hospital. By asking the relevant clinical staff to select the primary outcome for TREC-Lebanon we hoped to ensure maximum compliance with the trial protocol. Therefore, upon injection of the patient, a timer is started on the resident's phone and this rings at 20 minutes and then again at 40, 60 and 120 minutes. At each period the attending resident rates whether the person is tranquil, asleep, has shown adverse effects or needs additional treatment (see Appendix H). This attending resident is not blinded. The person is considered tranquillised when they are

felt to be calm and peaceful, but not asleep. They should not be agitated or restless, nor displaying threatening verbal behaviour, physical aggression against objects, self-aggression or physical aggression to other people. Blinding this rater for every participant would have added additional complexity to the study that would have made the trial unacceptable to the emergency room staff. More importantly, it would have completely changed the emphasis of TREC-Lebanon. What is being evaluated is the real-world practice of giving two different drug regimens in the psychiatric emergency setting. In the real-world situation health care professionals know what treatment is being given.

In addition, nurse volunteers should they choose to participate can be an additional rater, blind to allocated treatment who will, unknown to the health professionals looking after the patient, time the period between injection and tranquillisation and / or sleep exactly. These data will be used to validate the rating of the follow up form (see Appendix H). Additional data are then recorded at 24 hours and finally at two weeks (See Appendix H).

All additional data are to be extracted from routine notes. If the person is transferred to another hospital, the co-ordinating

centre will contact every hospital to find out further details on outcome after transfer.

5.4.8 Data collection, entry and analysis

All data for TREC-Lebanon will be collated from the TREC-envelope forms and routine notes of each emergency room or ward (See Appendix H). These data, in compliance with the Nottingham ethics committee requests, will be protected via anonymising the personal data of trial participants. The data will be inputted onto Microsoft Access (Or a program of similar nature).

Analysis will take place within this package and SPSS. Tables for this analysis are prepared before recruitment of the first patient (See Appendix I). All analysis will be based on groups as randomly allocated; this will be an intention-to-treat analysis. For the principal comparisons statistical significance will be taken at a 5% level, to minimise the impact of multiple comparisons. Relative risk, risk difference and 95% confidence intervals will be estimated for tranquillisation by 20 (Primary outcome), 40 and 60 and 120 minutes (Secondary to primary outcome). For simplicity, SPSS will primarily be used to run frequency tables. Revman will be used to calculate risk ratios and confidence intervals between interventions.

5.5 Anticipated risks

In the following subtopics I will discuss all the risk associated with the TREC-Lebanon along with how these will be assessed and mediated.

5.5.1 Ineligible people entering the study

It is possible though highly improbable that patients who do not fit the trial's entry criteria may enter the study. Those that do will not be counted as part of the trial and their notes will be disregarded. Detecting ineligible patients will be seen in the data entry form left at the director of research's office (SH) making it simple and direct to trace.

5.5.2 Staff compliance with protocol

Attending resident and nurse should monitor action of given intervention i.e. make sure given treatment has been injected properly. In the event that an agitated patient may break any of the treatment tools – mainly the syringe containing the treatment intervention or destroy the vial containing the intervention before being placed within the syringe, another TREC envelope should *NOT* be opened. Instead, attending resident should carry on as per hospital protocol and fill out the serious event form detailing the circumstances (See Appendix H). Nurses should also detail the nature of compliance, as they would normally do in their notes. In the

event a patient does break the syringe or capsule, the situation is rectified with the nurse bringing the emergency treatment as detailed in the paper slip in the envelope.

5.5.3 Feasibility phase

A feasibility phase will take place before the trial commences. The feasibility phase will include a limited number of envelopes (5) with contents known to the trialists. The feasibility phase is designed to test the trial's procedure in practice in order to assess if any unforeseen circumstances arise. In the event such unforeseen circumstances do arise, the trialists will rectify and mediate in the most practical way possible. Changes will be noted by the head researcher (JD) and updated in the trial protocol.

5.5.4 Additional envelopes

Ineligible people entering the study (see above) are at risk of using trial envelopes designed for patients eligible for the trial only. This ultimately affects the balance of both intervention samples therefore one solution is that a limited number of TREC-Lebanon envelopes will be crafted or bought for the trial beforehand and will be placed in SH's secure office to ensure the trial has a balanced sample between two groups.

5.5.5 Toxicity and serious unexpected events

After trial entry, clinical events are recorded, as usual, in the patients' notes. Complications and adverse events should be managed as usual. A serious unexpected event form (Appendix H) is provided and will be sent to the TREC-Lebanon Co-ordinator (JD) as soon it is completed. As mentioned in the eligibility criteria above, the attending doctor retains the right to withdraw the patient and the Steering Committee evaluates the overall circumstances of the event. In the event toxicity levels are more prevalent than anticipated, the Steering Committee may terminate the trial.

5.6 Trial organisation

The TREC-Lebanon Co-ordinating Group: The co-ordinating centre of the Lebanese arm is based at the Institute of Mental Health University of Nottingham United Kingdom. The Co-ordinating Group has overall responsibility for the design of the proposed trial and is responsible for all aspects of day to day trial administration. The Co-ordinating team is also responsible for preparing reports for the steering committee. Membership: Joseph Dib, Clive E Adams, Souheil Hallit.

5.6.1 Steering Committee

The overall progress of the trial, adherence to protocol, patient safety and the consideration of new information will be

monitored by a scientific and administrative Steering Committee. The membership of this committee is PS and RH.

5.6.2 Data Monitoring Committee

TREC-Lebanon will include a committee to oversee progress of the trial. Since TREC-Lebanon might take three to six months to complete, an independent data monitoring committee (DMC) will, in confidence, monitor results. This could be undertaken on a week to week or month to month basis depending on the collective agreement of all the members of the DMC. In the light of the interim data, and of any other evidence or advice they wish to seek, the DMC will inform the chair of the Steering Committee (PS) if, in their view: i. there is proof beyond reasonable doubt that for any particular group or subgroup treatment with one or other regiment is clearly indicated or contraindicated or: ii. it is evident that no clear outcome will be obtained. Proof beyond reasonable doubt may be taken as the difference of at least three standard deviations and at least one of the primary outcomes.

The DMC may communicate certain interim analysis to the SC or suggest certain protocol changes, but the Steering Committee will remain responsible for deciding which changes to adopt. The membership of this committee is: GA and JM. The committee will receive the first batch of data when trial

participants are at a total of 50 along with information such as adverse effects, unforeseen circumstances and trial progress so far.

5.6.3 Funding

No participating centre will directly receive funds for involvement in TREC-Lebanon. By design, funding for the overall project is minimal. All funding is intramural and everyone involved is undertaking this project as part of their usual employment.

5.6.4 Proposed policy for publication and authorship

The success of the TREC-Lebanon trial depends on a collective collaboration of multiple people in different professions working in the hospital. As TREC-Lebanon trial is formulated as part of a PhD thesis program at the University of Nottingham, Joseph Dib is listed as primary author. However, due to the large number of people that may be involved in the study, general publication may not be able to name everybody that has contributed in minor ways to the study. Authorship will depend on the substantial input onto the study. Every effort will be made to name everyone who has made such an effort within a collective authorship (the TREC-Lebanon Collaborative Group). The trial co-ordinator (JD) and research director of Deir Salib Hospital Souheil Hallit will meet to discuss principle

authorships and potential journals of publication before final report is published.

5.6.5 Access to data

Once the study is completed, access to study and all its data will be anonymised and accessible as part of JD's final thesis draft. All data is protected as per regulations of the Psychiatric Hospital of the Cross and Lebanese Law.

5.7 Acknowledgments

5.7.1 Thanks

The authors acknowledge the work and efforts of the TREC-Collaborative Group – some not listed as authors - to which this trial took permission, acceptance, study design and initiative in order to carry out TREC-Lebanon.

The authors acknowledge the efforts of all employees at 'Deir Salib Hospital' Hôpital Psychiatrique De La Croix including all researchers, physicians, residents and nurses whose partaking in the trial made it possible.

The author acknowledges all the efforts of the University of Nottingham and in the Institute of Mental Health facility where this study was planned and passed onto ethics for approval.

5.7.2 Competing interests

The research co-ordinator JD declares none.

5.7.3 Prior beliefs

Clive Adams did not foresee a noticeable difference between HP and HPC while Joseph Dib believed HPC would have greater benefits than HP.

6. Chapter VI- TREC-Lebanon

6.1 Background

The preparation for, and design of the protocol for TREC-Lebanon are described in the preceding chapters. Apart from the more conventional aims of evaluation of treatments, TREC-Lebanon aimed to:

- Highlight another 'local' difference in practice where it comes to treatment of people with acute aggression (the use of the triple drug combination);
- Further demonstrate how interested clinicians can design and undertake a randomised study which is practical, informative and rewarding despite shoe-string funding – albeit with limitations (Lede, 1999); and to
- Showcase, again, how sites of less well funded mental health care in low- or middle-income countries – and this time from the Arab world – can nevertheless, undertake evaluative studies of wide importance.

There were considerable difficulties in the conduct of this trial experienced both locally in Beirut and in the UK. TREC-Lebanon did not aim to – but also served to - teach this researcher many [not so easy] lessons for the future. This chapter will present the results of TREC-Lebanon with some

discussion leaving some more issues to be considered in Chapter VII. The final chapter (VII), however, will also discuss the problems TREC-Lebanon highlighted with local ethics decision pathways and how the conduct of the trial revealed flaws in the trial design – and how both were overcome.

The short feasibility phase ran from the 8th-18th of September 2018. This short non-randomised phase tested TREC-Lebanon's procedural systems (see Protocol) – and served to familiarise clinicians with the simplicity of the trial – in the hope of assuaging any remaining concerns. The feasibility phase was a success. Five people were treated during this time and the residents modified the design as it was more sensible for them to *carry* the TREC envelopes with them at all times rather than keeping them in the residents' office.

Official trial commencement was on the 19th of September 2018. The trial ran from this date to July 1st, 2019 when it reached its target of 100 participants. Eight residents, two groups of four across the training rotation of 2018-19, oversaw the trial.

6.1.1 Hypothesis

The null hypothesis states if that there is no clear (statistically different) difference between the HPC and HP regimens for the primary outcome of calm/tranquil at 20 minutes.

6.2 Methods

For full details of the methods please see Chapter V.

6.2.1 Setting

TREC-Lebanon was conducted at the Hopital Psychiatrique De La Croix (Psychiatric Hospital of the Cross), Beirut, Lebanon. The psychiatric hospital is open 24 hours a day. Unlike other TREC trials, the Psychiatric Hospital of the Cross does not have an emergency room. People are brought in by friends, family or law enforcement and admitted through an admission office. Violent/aggressive people are taken by trained nurses to a designated ward (based on their insurance). TREC-Lebanon, designed not to interfere with routine care, took this into consideration.

6.2.2 Selection of patients

Patients who were admitted directly into the hospital, or by transfer from another clinic, were candidates for TREC-Lebanon. Eligibility criteria included those who were 18 and above, up to 65 years of age and who displayed an aggressive episode requiring rapid tranquilisation. Patients were not eligible if the attending clinician believed any of the interventions were a potential risk to this particular patient, if consent was withheld by relatives or if the patient was already in the trial.

6.2.3 Randomisation and intervention

Randomisation, undertaken using a computer-generated system, was undertaken in the UK (by CEA) and codes were sent to the Director of Research in Lebanon (SH). Randomly ordered, randomly sized small blocks were used, stratified by male and female. Seventy envelopes were prepared for men, 30 for women. The decision to include a higher a male ratio was because the survey (Chapter III) showed higher frequency of aggressive episodes for men.

Interventions were either IM haloperidol plus promethazine or IM haloperidol plus promethazine plus chlorpromazine. Doses were at the discretion of the attending clinician.

6.2.4 Procedures

Unlike previous TREC trials (Huf, Coutinho, Adams, & trial, 2002), TREC-Lebanon did not utilise boxes with forms and medication included within. Instead, A4 size envelopes were used. Each envelope was titled with its appropriate TREC ID number with all TREC forms included within while the TREC entry form is printed onto *the outside* of the envelope. Inside the TREC envelope was a smaller fully opaque envelope (A6 size) containing the name of the intervention written on paper. As randomisation was stratified by sex, each resident carried a pair of envelopes (one 'male' and one 'female') in their

consecutive orders. In the event of an agitated episode, the resident on duty on that particular day is in charge of delivering rapid tranquilisation. Should the person have been eligible, the resident proceeded to fill out the TREC entry form on the closed envelope, and only then opened the TREC envelope. This action entered the person into the trial. Then the resident proceeded to open the second envelope containing the name of the allocated intervention.

At this point, the resident doctor prescribed the medication at the doses felt to be appropriate and the nurses administered the intervention. At the point of administration, for which the resident is present, the resident started a personal timer that alerted at 20, 40, 60 and 120 minutes post intervention – corresponding to the boxes and intervals noted on the TREC-Lebanon primary measure of outcome form. Should there have been *any* adverse reactions, the envelope also contained an adverse event form.

The Brazilian and Indian TREC trials had one additional timing check – a medical student with a stopwatch to surreptitiously time the period between injection and tranquillity. This served to cross-validate the nurses estimates of tranquil/calm at the designated times. In the Brazilian and Indian trials nurses' estimates of period to tranquillity tallied closely with the

surreptitious stopwatch timings. In TREC-Lebanon, because so few staff were available, this form could not be used in the same way and residents were asked to note, on this additional form, a 'true tranquilisation' time – not one constrained by the 20, 40, 60, 120 minute boxes. In this way, if the aggression/disturbance surpassed the 2-hour interval, the resident could note the time the patient did eventually become tranquil or asleep.

Once the primary measure of outcome form was completed, the TREC envelope - along with the forms - were returned to the Research Director's office and secured in a safe. The resident then collected the next TREC envelope - in strict consecutive order – and, when necessary, repeated the process.

6.2.5 WhatsApp Group

Figure 6.1: Residents' Whatsapp group

A variation from the original TREC-Lebanon protocol was the formation of a TREC-Lebanon WhatsApp group for group correspondence. WhatsApp is a freeware, cross-platform messaging/voice over IP service. It allows users to send text and voice messages, make voice and video calls, and share images and documents. Since I was based between Lebanon and UK (2 hour time difference) and residents had many different duty times, a WhatsApp group was formed. This included the Research Director (SH) and allowed free communication, question answering, support and monitoring of progress. When a person was randomised, the resident alerted the WhatsApp group.

This helped keep track of numbers being randomised and any real or anticipated difficulties and the solutions. Every first of the month, the lead resident posted the duty schedule of each resident working in the trial which was shared on the WhatsApp group as well as in the residents' office.

6.2.6 Data acquisition

Data relevant to the trial were divided between patients' case notes and the TREC envelopes. I (JD), therefore, acquired data in two steps: first, extracting all from the TREC envelopes and putting these into the TREC-Lebanon data sheet on Microsoft Excel. The TREC envelopes contained all TREC forms

(characteristics of patients at trial entry, primary measures of outcome, secondary measures, etc.). Remaining information such as date of birth, diagnosis, drugs used, etc. were located in patient case files. The second step, therefore, was to extract these data from files located in the hospital's archives (if the patient was discharged). If patient was not discharged, I acquired the patient case file from their ward where they were being treated. These steps were undertaken by visiting the hospital for four one-week periods over the trial's 10-month run – usually when approximately a new quarter of the 100-number target were randomised. In undertaking direct visits, I hoped to maximise time efficiency, oversee trial running, motivate residents and maintain good relations and *espirit de corps*. A CD-ROM containing *anonymised* TREC-Lebanon MS Excel datasheet is attached to this thesis.

6.2.7 Data analysis

Review Manager 5.3 (Review Manager, 2014) and IBM SPSS 25 (Statistical Package for Social Sciences) (IBM Corp, 2017) were used for data analysis. For primary measures and secondary measures of outcome, RevMan was used to calculate Risk Ratio (RR) and 95% Confidence Intervals (CI). This is different to what is stated in Chapter V RevMan 5.3 was used because of its reliability and simplicity. SPSS was used to

run frequencies on other outcomes such as characteristics of patients, treatment compliance and clinical outcomes.

6.3 Results

6.3.1 Characteristics of patients at trial entry

Across the 10-month period of recruitment to gain 100 participants the survey (Chapter III) predicted that around 400 people would have been eligible for TREC-Lebanon (survey had 1.26 people per day who were aggressive, ~300 days study duration, predicted number therefore = 378). The data recorded for those who were aggressive but not entered into the trial across the period of recruitment were handwritten. These were not easy to decipher/interpret but do seem to fall into several distinct categories which, broadly, could explain much of the slower than predicted recruitment to TREC-Lebanon. For the first half of the trial, three days were covered by residents who were not taking part in the trial. For the second half of TREC-Lebanon this fell to two days per week. So, in reality, of the 300 days of recruitment only 193 were covered by doctors bringing people into the trial. At the survey-predicted rate of recruitment this would then suggest 244 people should have been eligible yet only 100 were really entered. Deciphering the reasons for people not being entered the frequency of people within the broad categories does seem

to account for the loss of around 144 nearly eligible people. A sizable group fell outside the age range – being either over 65 year of age or under 18. Another large group had insurance cover that did not cover their medical bills and hospital care. Other categories were a group of people already sedated or proceeding towards sedation from treatment administered before reaching the hospital, a small group of people who the doctors were not happy to randomise for various reasons and, finally some people who either were simply mistakenly not randomised, or for whom the reason not to enter remains a mystery. TREC-Lebanon recruited, approximately 1 in 2 of the truly eligible. Of the 100 participants randomised, two left the hospital and their data were withdrawn. Family members decided that they did not want their relative to be part of the trial and there was no more involvement and their data were withdrawn. Four people, again, post-randomisation, withdrew consent for participation and all their data were also withdrawn.

Table 6.1: CONSORT flow diagram

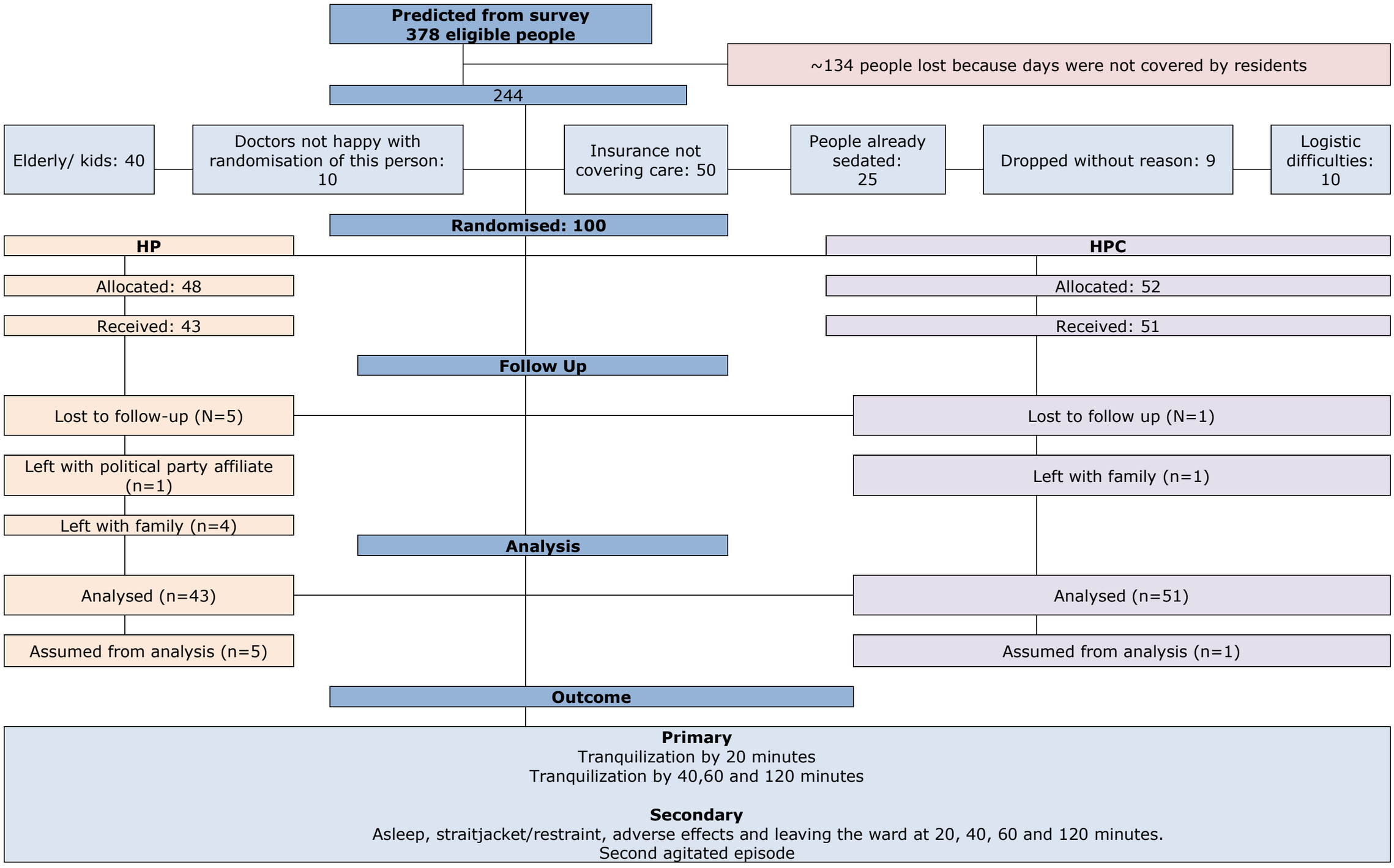


Table 6.2 shows basic information collected at point of randomisation with the presumed causes for the disturbance recorded blind to group of allocation (before the envelope was opened).

Table 6.2: Characteristics of patients at trial entry

		HP	HPC
Randomised	**Total**	**48**	**52**
	Withdrawn	5	1
	Completed	43	51
Characteristics			
Age			
	Mean	36 (SD: 12.3)	37 (SD 11.4)
	Median	35	36
Sex		**N (%, 95% CIs)**	
Male	Total 45	21 (44%, 30-59)	24 (46%, 32-60)
Female	Total 49	22 (46%, 32-61)	27 (52%,37-66)
Missing		5 (10%, 4-22)	1 (2%, 0-10)
First psychiatric attendance			
Yes		23 (48%, 34-63)	33 (63%, 50-75)
No		20 (42%, 28-57)	18 (35%, 22-49)
Missing		5 (10%, 4-22)	1 (2%, 0-10)
Severity of disturbance - first impression			
Moderately		4 (8%,3-19)	1 (1%,0-10)
Markedly		16 (33%, 21-48)	18 (37%, 24-51)
Severely		20 (42%, 29-56)	32 (61%, 48-74)
Among the most extreme disturbed		3 (6%, 2-16)	0 (0%, 0-8)
Missing		5 (10%, 4-22)	1 (1%, 0-10)
Presumed cause for agitation			
Psychosis (schizophrenia or mania)		27 (56%, 42-70)	30 (58%, 44-70)
Substance abuse		5 (10%,4-22)	3 (6%, 2-16)
Intellectual disability		1 (2%, 0-10)	3 (6%, 2-16)
Clinical organic (Metabolic, hormones, etc.)		0	0
Psychological		0	1 (2%, 0.1-12)
Unknown		10 (21%, 11-34)	14 (26%, 17-40)
Withdrawn		5 (11%, 4-22)	1 (2%, 0.1-12)
Already on antipsychotic medication			
Yes		41 (85%, 72-92)	44 (85%, 71-93)
No		2 (5%, 1-13)	7 (13%, 6-26)
Withdrawn		5 (10%, 4-22)	1 (2%, 0-10)

Most of the people randomised were in their 30s. The experienced staff thought this group to be really quite disturbed and that the disturbance was most frequently due to a psychotic illness (schizophrenia or mania) despite the majority already being on antipsychotic drugs. Substance misuse as a primary cause of disturbance seems uncommon. Approximately half of the participants were women and half were experiencing their first psychiatric attendance – although most of both groups were already on antipsychotic drugs. Baseline characteristics are evenly distributed between the two groups of allocation.

Table 6.3: Non-emergency drugs as part of routine treatment

Category	Drug name	HP	HPC	RR	CI
Antipsychotics	Aripiprazole	3	2		
	Chlorpromazine	15	24		
	Clozapine	8	3		
	Haloperidol	5	11		
	Olanzapine	10	6		
	Paliperidone	1	1		
	Risperidone	8	13		
	Quetiapine	5	11		
	Any	**41**	**45**	**0.99**	**[0.84, 1.16]**
Benzodiazepines	Clonazepam	3	2		
	Lorazepam	13	12		
	Diazepam	5	10		
	Any	**25**	**29**	**0.93**	**[0.65, 1.34]**
Anticholinergics	Promethazine	15	29		
	Trihexyphenidyl	6	7		
	Any	**15**	**29**	**0.56**	**[0.35, 0.91]**
Mood stabilizers	Carbamazepine	2	1		
	Gabapentin	1			
	Phenytoin		1		
	Pregabalin	1			
	Topiramate	1			
	Valproic acid	8	21		
	Lithium $C0_3$	11	10		
	Any	**21**	**31**	**0.73**	**[0.50, 1.09]**
Antidepressants	Fluoxentine	2			
	Sertraline	2	1		
	Venlafaxine	1			
	Any	5	1	5.42	[0.66, 44.72]
Various others	**Any**	12	12	1.08	[0.54, 2.18]
Total	**Any**	**45**	**44**		

Non-emergency drugs were prescribed as part of the normal treatment regimen (See Table 6.3: Non-emergency drugs as part of routine treatment). A total of 89 patients were already prescribed non-emergency drugs with 45 being in the HP group and 44 being in the HPC group. Drug classes were evenly distributed. It is feasible that the routine prescription choice was influenced by the drug regimen of allocation but there is no indication of this.

A total of 100 patients were allocated with 48 in the HP group and 52 in the HPC group. Although the dosages of allocated drugs were at the discretion of the prescribers, there was no variation – in effect, every person entering the trial received 5mg of haloperidol and 25 of promethazine given by intramuscular injection. In addition, the HPC group were given chlorpromazine (100mg IM).

Table 6.4: Compliance with protocol

		HP (n = 48)	HPC (n = 52)
Progressed through trial		43 (90%, 73-93)	51 (98%, 88-99)
Received allocated treatment	Yes	43	51
	No	0	0
Withdrawn		5 (10%, 4-22)	1 (2%, 0.3-10)
Received allocated treatment	Yes	1	1
	No	4	0

Unsurprisingly, very high proportions of those allocated the treatments received them as per protocol. Six families

withdrew consent to record their data. Five from the HP group. Four of this small group left for unclear reasons, and one was withdrawn by insurance representatives from Hezbollah - the person's political affiliate group. One person from the HPC group had data withdrawn at the family's request.

For those who did not receive the medication of allocation or withdrew their consent to record/use their outcomes I assume an outcome similar to that of the allocated group overall. This allows ITT analysis. For the key outcomes (binary - tranquil/calm at specified time periods) ITT analyses were compared with analyses of people who both received the treatment of allocation and for whom all data were collected ('per protocol' analyses).

6.3.2 Placement

Most people were treated in the ward environment (n=94, 100% per protocol participants).

Table 6.5: Immediate placement

	HP (n = 48)	HPC (n = 52)
Transferred to ward	43 (90%, 77-95)	51 (98%, 89-99)
Left with family	4 (8%,3-19)	1 (2%, 0-10)
Other (left with Hezbollah – special insurance)	1 (2%, 0-10)	0 (0%,0-6)

6.3.3 Primary measure of outcome – tranquil or calm

Primary measure of outcome was at 20 minutes post intervention. Whether the analyses were ITT, even with more extreme assumptions of ITT 2 and ITT3, or only for those who received the medications for whom permission to gather outcome data had been given, results showed no clear differences between the two intervention groups when assessing rapid tranquilisation. Around one third of both groups were tranquil or calm by 20 minutes (30% CI 21-40).

Table 6.6: Primary measure of outcome - calm or tranquil

20 mins	HP		HPC		RR [CI]
	Event	Total	Event	Total	
ITT 1	**14**	**48**	**18**	**52**	**0.84 [0.47, 1.50]**
ITT 2	18	48	18	52	1.08 [0.64, 1.83]
ITT 3	13	48	19	52	0.74 [0.41, 1.33]
Per protocol	13	43	18	51	0.86 [0.48, 1.54]
Total missing		5		1	
40 mins					
ITT 1	**25**	**48**	**41**	**52**	**0.66 [0.49, 0.90]**
ITT 2	29	48	40	52	0.79 [0.60, 1.03]
ITT 3	24	48	41	52	0.63 [0.46, 0.87]
Per protocol	24	43	40	51	0.71 [0.53, 0.96]
Total missing		5		1	
60 mins					
ITT 1	**35**	**48**	**45**	**52**	**0.84 [0.69, 1.03]**
ITT 2	39	48	44	52	0.96 [0.80, 1.1.5]
ITT 3	35	48	45	52	0.84 [0.69, 1.03]
Per protocol	34	43	44	51	0.92 [0.76, 1.11]
Total missing		5		1	
120 mins					
ITT 1	**35**	**48**	**47**	**52**	**0.81 [0.66, 0.98]**
ITT 2	39	48	46	52	0.92 [0.78, 1.09]
ITT 3	35	48	47	52	0.81 [0.66, 0.98]
Per protocol	34	43	46	51	0.88 [0.73, 1.05]
Total missing		5		1	

ITT 1	Those missing same proportion of events as those who stayed in
ITT 2	Those missing in HP all tranquil, those in HPC not tranquil
ITT 3	Those missing in HP not tranquil, those missing from HPC all tranquil

By 40 minutes, however, there did seem to be a clear – and important (18%) - difference between groups. Around 25% (CI 17-34) of those allocated to HP were tranquil compared with 43% (CI 33-53) given the triple therapy. This statistically significant difference (RR 0.66 CI 0.49, 0.90) stayed relatively stable across the different assumptions. By 60 minutes, more people in the haloperidol + promethazine group were tranquil or calm – narrowing the difference between the groups to not being convincingly statically significant, with the same applying at the 120-minute mark. By then well over 80% (CI 71-87) of people were tranquil or calm.

6.3.4 Secondary measures of outcome – 1 – asleep or restricted

Table 6.7: Secondary measures of outcome 1 - asleep or restricted

Asleep	**HP (n=48)**		**HPC (n =52)**		**RR (95% CI)**	
	Event	Total	Event	Total		
By 20 minutes						
ITT 1	**2**	**48**	**0**	**52**	**5.41**	**[0.27, 109.87]**
ITT2	7	48	0	52	16.22	[0.95, 276.65]
ITT3	1	48	1	52	1.08	[0.07, 16.84]
Per protocol	1	43	0	51	3.55	[0.15, 84.86]
Total missing		5		1		
By 40 minutes						
ITT 1	**9**	**48**	**9**	**52**	**1.08**	**[0.47, 2.50]**
ITT2	13	48	8	52	1.76	[0.80, 3.87]
ITT3	8	48	9	52	0.96	[0.40, 2.29]
Per protocol	8	43	8	51	1.19	[0.49, 2.89]
Total missing		5		1		
By 60 minutes						
ITT 1	**10**	**48**	**25**	**52**	**0.43**	**[0.23, 0.81]**
ITT2	14	48	24	52	0.63	[0.37, 1.07]
ITT3	9	48	25	52	0.39	[0.20, 0.75]
Per protocol	9	43	24	51	0.44	[0.23, 0.85]
Total missing		5		1		
By 2 hours						
ITT 1	**18**	**48**	**24**	**52**	**0.81**	**[0.51, 1.30]**
ITT2	22	48	23	52	1.04	[0.67, 1.60]
ITT3	17	48	24	52	0.77	[0.47, 1.24]
Per protocol	17	43	23	51	0.88	[0.54, 1.41]
Total missing		5		1		
Straitjacket +/- restraint						
By 20 minutes:						
ITT 1	**16**	**48**	**17**	**52**	**1.02**	**[0.58, 1.78]**
ITT2	21	48	15	52	1.52	[0.89, 2.59]
ITT3	16	48	16	52	1.08	[0.61, 1.92]
Per protocol	16	43	15	51	1.27	[0.71, 2.25]
Total missing		5		1		
By 40 minutes:						
ITT1	**13**	**48**	**10**	**52**	**1.41**	**[0.68, 2.91]**
ITT2	18	48	9	52	2.17	[1.08, 4.35]
ITT3	12	48	10	52	1.30	[0.62, 2.73]
Per protocol	12	43	9	51	1.58	[0.74, 3.39]
Total missing		5		1		
By 60 minutes:						
ITT1	**9**	**48**	**8**	**52**	**1.22**	**[0.51, 2.90]**
ITT2	13	48	7	52	2.01	[0.88, 4.62]
ITT3	8	48	8	52	1.08	[0.44, 2.66]
Per protocol	8	43	7	51	1.36	[0.53, 3.43]
Total missing		5		1		
By 120 minutes:						
ITT1	**5**	**48**	**6**	**52**	**0.90**	**[0.29, 2.77]**
ITT2	9	48	5	52	1.95	[0.70, 5.41]
ITT3	4	48	6	52	0.72	[0.22, 2.40]
Per protocol	4	43	5	51	0.95	[0.27, 3.31]
Total missing		5		1		

As for the more extreme – but also the more concrete - outcome of 'asleep' – as opposed to 'tranquil or calm' – events were less common in both groups, but, again, with no clear difference at 20 minutes. By 40 minutes around 20% (CI 13-28) of both groups were asleep. At the one-hour mark, statistically significantly more people in the HPC group had fallen asleep but by two hours this difference had disappeared with around half of both groups being asleep – 45% (CI 32-52).

The use of restraints and or straitjackets is now well documented in Lebanese practice (Dib et al., 2018). It is part of routine care. At no stage was there an impression that one or other medication regimen influenced the use of this form of restriction. Initially (at 20 minutes) around 30% (CI 21-40) in both groups were restrained in this way. By two hours this had decreased to approximately 9% (CI 4-16) in each group.

6.3.5 Secondary measures of outcome – 2 - recurrence

Recurrence of agitation thought to be part of the index episode was a secondary outcome. As a discrete outcome, this was not recorded to have occurred.

Table 6.8: Secondary measures of outcome 2: Recurrence

Recurrence of agitation – thought part of index episode - after a period of initial settling		
	HP	**HPC**
By 20 minutes	0	0
By 40 minutes	0	0
By 60 minutes	0	0
By 120 minutes	0	0

However, prescribing of additional emergency non-routine treatments, *up to 12 hours* post-randomisation were also well-recorded as part of the on-going emergency episode (see Appendix K). Some of this non-routine prescribing was of anticholinergic drugs which I have taken as indication of need to offset adverse effects, but the non-routine *antipsychotic* prescribing seems likely to indicate some additional problem or anticipation of additional problem.

Table 6.9: Non-routine antipsychotic drugs after randomisation

Category	**Drug Name**	**HP**	**HPC**	**RR**	**CI**
Antipsychotics	Chlorpromazine	2			
	Haloperidol	1			
	HP	1	4		
	HPC	2	3		
	Quetiapine	3			
	Zuclopenthixol +promethazine	1			
	Zuclopenthixol acetate	2			
	Any	**10**	**7**	**1.55**	**[0.64, 3.74]**

The experienced clinicians felt that some in both groups should be given additional antipsychotic drugs outside of their routine prescriptions – but, again, there was no indication that one or other of the randomly allocated drug regimens really resulted in a different prescribing pattern (18% CI 9-24 in both groups).

Table 6.10: Non-routine benzodiazepines after randomisation

		HP	HPC	RR	CI
Benzodiazepines	Clonazepam	1	0		
	Diazepam	5	5		
	Lorazepam	6	3		
	Any	**11**	**8**	**1.63**	**[0.73, 3.63]**

Benzodiazepines were the most commonly prescribed pharmacological treatment used as emergency add on treatment – but, again, there was no clear difference between the HP and HPC groups (RR1.63, CI 0.73, 3.63).

Table 6.11: Non-routine non-pharmacological emergency treatment after randomisation

		HP	HPC	RR	CI
ECT	Scheduled for emergency ECT	0	1		
Straitjacket	Straitjacket	3	2		
Total	**Any**	**3**	**3**	**1.08**	**[0.23, 5.11]**

'Prescribing' of non-pharmacological new adjunctive treatments within the 12 hours was not common and again, with no indication of any difference between the two groups.

6.3.6 Secondary measures of outcome– 3 – new agitated episode

New agitated emergency episodes were noted down 12 hours after randomisation.

Table 6.12: New agitated emergency episodes

New episode – beyond 12 hours	HP	HP C	RR	CI
Yes	**11**	**12**	**0.99**	**[0.48, 2.04]**
No	32	39	0.89	[0.69, 1.15]

Approximately one third (32%) of all participants randomised had another new agitated episode at least 12 hours after randomisation with no significant disparity between both groups (RR0.99 CI 0.48, 2.04).

Table 6.13: Proxy measure for new agitated episode - antipsychotics used

Second – new - agitated episode (agitated episode post 12 hours)				
	HP	**HPC**	**RR**	**CI**
Zuclopenthixol +/- promethazine IM	3	4		
HPC IM	4	2		
HP IM	2	1		
Promethazine + Chlorpromazine IM	1	0		
Other – unclear	2	4		
Any	**12**	**11**	**1.18**	**[0.58, 2.42]**

Antipsychotic treatments were the main regimen used for these new agitated episodes with zuclopenthixol being the most favoured. There were no significant differences between the HP and HPC groups (RR1.18, CI 0.58, 2.42).

6.3.7 Secondary measures of outcome – 4 – adverse reactions

The adverse event sheet within the TREC-Lebanon envelope was not used. Certainly, this was not part of routine care and residents simply did not use this to record any outcomes. Its use had been discussed, agreed and implemented at design and protocol stage. It just was not used in the real-world circumstances.

Two further sources of information remained – the notes of each person and the drug prescription card. No adverse events were recorded in the notes but the use of the anticholinergic drug – trihexyphenidyl – gives some indication of anticipated and occurring extrapyramidal problems. The prescription records are good and fall into two categories. First there is where trihexyphenidyl was prescribed in any situation and second where the drug was given as non-routine. In both instances there is no indication that use of either regimen resulted in the need for this additional prescribing. Trihexyphenidyl is only given to offset extrapyramidal effects

and promethazine commonly so. However, the latter, with its histaminic properties, also sedates.

Table 6.14: Adverse reactions - proxy measures used

Adverse reactions – within index episode				
	HP	**HPC**	**RR**	**CI**
Any recorded on TREC sheet	0	0		
Any recorded in notes	0	0		
Proxy - use of trihexyphenidyl overall	6	8	0.89	[0.33, 2.36]
- Non-routine use of trihexyphenidyl	0	1	0.39	[0.02, 9.43]
- Promethazine	1	2	0.59	[0.06, 6.32]
Any	**1**	**3**	**0.36**	**[0.04, 3.35]**

One person allocated to HP had completed her period in hospital and after one month died from a cardiac event. This sad event was carefully considered by all relevant on the research team, the resident and the Director of the hospital. There was no indication that there was any connection with TREC-Lebanon.

6.3.8 Secondary measures of outcome – 5 - others

The initial diagnosis had been made with very little history in the midst of the emergency. By the end of two weeks, trial participants had had much more clinician-time and their history and diagnosis was becoming clearer.

Table 6.15: Diagnosis – two-week follow up

	On arrival	By 2 weeks	
		Stable	Change
Primary diagnostic group	**Number**		
Bipolar	39	35	4
Schizophrenia	35	39	-4
Substance misuse	11	11	0
Depression	4	4	0
Learning disability	4	4	0
Epilepsy	1	1	0

The initial 'spot' diagnoses were remarkably stable with only four of those initially diagnosed as having schizophrenia being categorised as bipolar by 14 days.

6.4 Discussion

6.4.1 Characteristics of patients at trial entry

The rate of recruitment was much slower than that predicted by the survey. I feel that most reasons for the protracted period of recruitment, to the 100-participant cut off, can be understood and are listed in the CONSORT diagram above. Probably more residents would have taken part with more of a presence of the lead researcher (myself) on the ground. In this way less recruitment days would have been lost – and this was the major avoidable cause of slow recruitment. I could have done little when people were outside the age range and for whom insurance cover was problematic. Finally, perhaps, a

higher profile for the lead researcher might have helped avoid the administrative losses – or the ones for which reasons remain unclear. My absence from the front line of care was unavoidable and, certainly, my presence there would have hastened the completion of recruitment. However, the achievement of TREC-Lebanon in recruiting around every other eligible person, whilst running almost independent of the lead researcher in a hospital not at all used to running trials, remains a considerable achievement for the Hopital Psychiatrique De La Croix team.

The characteristics of people entering the trial were evenly distributed between groups indicating successful randomisation. People were, in the opinion of the experienced clinicians, very disturbed. There is no indication that fewer problematic patients were selected for inclusion in TREC-Lebanon. Most people were in their 30s and many were experiencing their first psychiatric attendance despite frequently being on antipsychotic drugs. This could indicate how the community service cares for many people with quite severe illness for considerable periods before the hospital is called upon to help. As the numbers of specialist psychiatrists per head of population in Lebanon is low (2/100,000; UK 8/100,000) these do not seem unreasonable assumptions. The presumed cause of the initial disturbance was most commonly

thought to be psychotic illness with this stable by the end of two weeks. Substance misuse was uncommon – certainly as a primary cause of the aggression. This diagnostic profile is similar to the previous TREC trials (Raveendran, Tharyan, Alexander, & Adams, 2007; TREC Collaborative Group, 2003).

What is more difficult to explain is the propensity of women. The survey predicted a 70:30 men-to-women split (Dib et al., 2018) and this would be in keeping with ratios in other countries (Denson, O'Dean, Blake, & Beames, 2018; Flannery, Wyshak, Tecce, & Flannery, 2014). It is possible that, although the people entering the trial were not clearly selected to be the less disturbed than usual care, aggressive women were seen as a safer option when choice of treatment was taken from the control of clinicians by entry into the trial. Wards where female patients stay solely have women staff. The severity of aggression as perceived by the residents (noted in the TREC-Entry Form) indicates women were perceived to have more violent outbursts in number than their male counterparts. It is possible the threshold for intervention is lower for female nurses compared to male nurses. Cultural factors may also have played a role. Although I do not have hard evidence of this, I speculate that Lebanese women are almost always living with a family or spouse - seldom alone – despite mental disturbance. Men with serious mental illness,

on the other hand – and, again, I speculate – may be more likely to be used to living less rooted in family and the uprooting into hospital could be less disturbing in itself. The minimal data collection of TREC-Lebanon precludes anything but speculation on these points. To attempt to investigate whether some selection was taking place that could have been a function of *clinician confidence* in the trial I plotted recruitment across time. I felt that confidence in the trial did seem to increase across the 10 months. The simple Figure 6.2: Male/ Female recruitment rate shows recruitment across the months but the ratio does stay largely stable. There is no hint that clinicians, unconfident at the start had a different differential recruitment by the end.

Figure 6.2: Male/ Female recruitment rate

In any event, whatever the cause of the larger than expected numbers of women, this means that TREC-Lebanon does provide some higher-grade evidence of the effects of treatments for aggression of this often-under-represented group.

6.4.2 Compliance with allocated treatment regimen

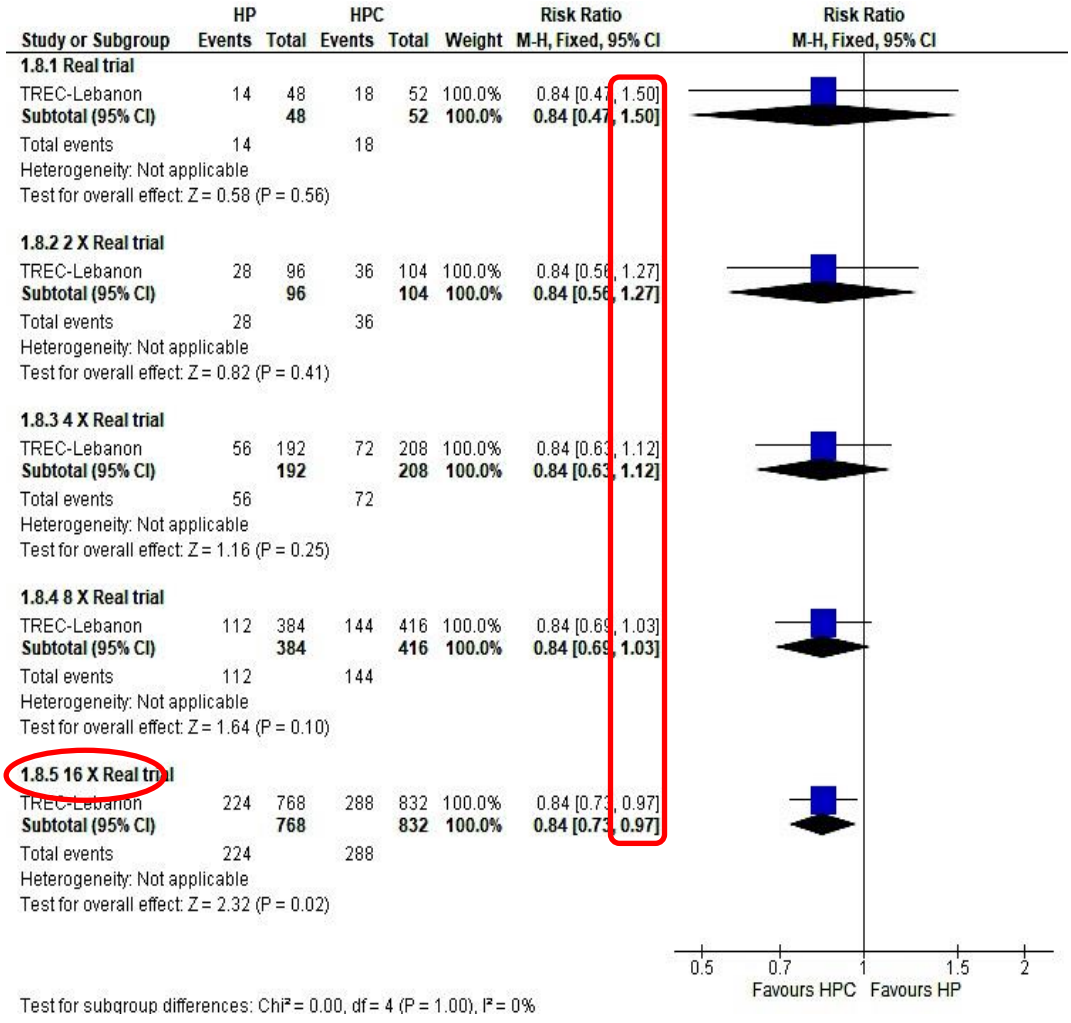
A total of 100 patients were allocated with 48 in the HP group and 52 in the HPC group, and, given the nature of the trial, the high compliance with treatment was to be expected. However, six people withdrew, and I have not used their data. I have, however, assumed outcome in order to preserve intention-to-treat analyses. In the analyses various assumptions were compared with the outcomes derived only from those who completed the trial and there was never a substantive difference. The slightly narrower confidence intervals resulting from the ITT would seem likely to be more precise estimate of the 'truth', whilst preserving randomisation of known and unknown confounders and not using data the families did not want me to use.

That one person was not given on-going permission to provide data by instructions of Hezbollah gives readers outside Lebanon some indication of the unusual circumstances of this trial.

6.4.3 Primary outcome

Primary measure of outcome was at 20 minutes post intervention. Around one third of both groups were tranquil or calm by 20 minutes (32% CI 23-41). There was the *suggestion* in the numbers that the HPC regimen is more calming, but the statistical significance of the finding varies depending on assumption used. Perhaps there is no real difference or, perhaps a more powerful trial would have highlighted a real difference. In the figure below (Figure 6.3: Forest plot of assumed sample size) I have kept exactly the same result but kept doubling the size of the trial. Only by the time TREC-Lebanon is multiplied by 16 does the finding reach conventional levels of statistical significance.

Figure 6.3: Forest plot of assumed sample size



By 40 minutes over half of both groups are calm and by the two-hour mark this rises to 80%. TREC-Lebanon was, indeed, underpowered. It does, however, give strong indication that the level of recruitment to gain necessary power would have been very considerable - with a sample size nearing 2000. Clearly, however, both regimens – in the context of the hospital care – are highly calming and are efficient in achieving this, and any difference, should it really exist, may not be clinically meaningful enough to necessitate such a trial.

6.4.4 Secondary outcomes

a. Asleep/restricted

Throughout the results for 'asleep' there is the persistent impression that the HPC combination is more inducing of sleep although this only really reaches conventional levels of statistical significance by one hour – and not consistently so across different assumptions. The difference disappears by 120 minutes. Certainly, it is clinically logical that the addition of chlorpromazine to the HP combination would add sedation and good to see that TREC-Lebanon helps quantify this for the first time.

As can be seen from the findings of Chapter III, some form of physical restriction is common in clinical practice in Beirut. There were never any clear differences in the proportions in these restrictions throughout the study with percentages falling from around 30% at 20 minutes to 10% for both groups at 2 hours. Again, the double therapy (HP) does not have convincing disadvantage to the triple treatment (HPC).

b. Recurrence

Recurrence episodes were defined as 'revving back up' episodes that occurred within the time intervals post randomisation from when the timer was started until the two-hour mark. These data were clearly recorded in the TREC-

forms filled out by the residents; there were no reported recurrent episodes between the 20-120-minute time intervals. However, such episodes did occur after the initial two hours and this was noted down up to a 12-hour mark. Any emergency episodes beyond the 12 hours were recorded as a 'second agitated episode'.

Antipsychotics, benzodiazepines and anticholinergic drugs as well as non-pharmacological likely prescribed as part of an emergency treatment were recorded. Around 25% of both groups received antipsychotic or benzodiazepine drugs for what was likely to have been a recurrence of the index episode's aggression. Being randomised to haloperidol plus promethazine conferred no clear advantage – or disadvantage – compared with the triple therapy group. Despite the impression that the triple therapy caused more sleep – or at least more profound sedation – this did not clearly offset being treated for recurrence of the aggression. The less sedating HP mix was just as effective.

c. New agitated episode

Second agitated episodes were attained and noted from patients' case files beyond the 12 hours of the index episode. Similar to the ongoing emergency episode, antipsychotic medications were the preferred treatments – but this time

with zuclopenthixol acetate IM becoming prevalent. This treatment has a longer half-life than any of the others (Chakravarti, Muthu, Muthu, Naik, & Pinto, 1990) and may be being used in recognition of this potency for difficult aggression. Again, however, there was no difference between the HP and HPC group in the occurrence of a new episode or use of emergency antipsychotic drugs beyond the 12 hours. So – again – the much more widely-researched HP is no less effective than the less well-researched HPC combination.

d. Adverse reactions

No one used the adverse event sheet within the TREC-Lebanon envelope. The design of adding this was after careful consultation, but the sheet was just not employed. It is known that the use of HP does have adverse effects (Haddad & Sharma, 2007; Kurz, Hummer, Oberbauer, & Fleischhacker, 1995; Yen, Lung, & Chong, 2004). In other settings these have been recorded. It would seem unlikely that people in Lebanon differ that much for those in Brazil, India or Iran (Huf, Alexander, Gandhi, & Allen, 2016).

Table 6.16: Trials of haloperidol plus promethazine - adverse effects

Study	Adverse effects: EPS	Serious adverse effect
Baldacara 2011	5/30	
Mantovani 2013	20/28	
TREC-RIO I		1/150
TREC-Rio II		1/153
TREC-Vellore I		0/100
TREC-Vellore II	0/150	1/150

The addition of chlorpromazine to this already proven potent combination would be unlikely to reduce any adverse effects. In trials where extrapyramidal effects are specifically sought, they are there to find – although incidence is very variable. For the HP combination, other trials report that serious events occur around 1/150. The adverse events being occurrence of fits. It is possible that TREC-Lebanon was too small for one of these to be experienced. Should a very serious event have occurred within the timescale of the trial it would have been obvious from the notes – hence the discovery of one patient dying one-month post randomisation. Although this unfortunate event was not related to the circumstances of the trial, this event was still discovered during data acquisition.

As it turned out, routine clinical practice and the design of TREC-Lebanon – and probably the unavoidable absence of myself from the daily front line - worked against good recording of adverse effects. This is something that should be

addressed in future designs. That adverse events, in the context of great physical disturbance due to serious mental illness, are not thought of as serious enough to record routinely could be an issue of training, or of the priorities of the staff in these highly stressed emergencies.

e. Others

The open knowledge of group of allocation could have affected the doses of drug actually given. This has not proved the case in the other TREC studies of Brazil or India but it remains a possibility. In Brazil and India the doctors did use their discretion and the doses of drugs did seem to be tailored to the needs of the patient and situation (Khalifeh, 2016) albeit not effected by original group of allocation. In TREC-Lebanon, however, despite pragmatic instructions to the prescribers, everyone got the same doses. The randomisation of the addition of 100mg IM of chlorpromazine (CPZ) to the stable doses of the haloperidol plus promethazine conferred no obvious benefits. The impression of additional sedation CPZ produced did not offset recurrence of aggression within the same episode, use of additional medications or appearance of what seemed to be a new episode of aggression or violence.

Again, it is remotely possible that the open knowledge of treatment would affect the final diagnosis by two weeks. There is no suggestion of this.

6.5 Summary

TREC-Lebanon evolved out of front-line survey and clinically relevant systematic review work. This trial was possible with the drive and commitment of the health care staff of a large mental hospital of a complex middle-income country set in a region without a strong tradition of evaluation of psychiatric care through use of trials. TREC-Lebanon ran on shoe-string funding. Ideal trail design had to be curtailed because of this.

TREC-Lebanon, nevertheless, *did* run. It did succeed in highlighting the routine use of [yet] another treatment regimen for people whose acute aggression is thought due to serious mental illness (HPC) – and [yet another] one that had never been tested before in randomised trials. TREC-Lebanon pitted that triple therapy against the much more widely used and tested HP combination. Few, convincing, clear differences were apparent. Where clinicians felt there was no contraindication to giving the drugs, when there was uncertainty which was better to use, then the less complex, globally tested HP was swiftly calming, usually causing the situation to become tranquil within minutes, with the

accompanying decline in need for restraint. Adverse effects were not recorded well in TREC-Lebanon but there was no indication that either regimen caused severe difficulties and it is clinically plausible that the less complex HP would also cause less unwanted effects.

6.6 Acknowledgements

I undertook all analyses, but these were checked by Dr Boliang Guo [medical statistician], Institute of Mental Health, University of Nottingham, to whom I owe a debt of gratitude. Many thanks to all clinicians and staff at the Psychiatric Hospital of the Cross Beirut (TREC-Lebanon Collaborative group) who made this trial possible. Final thanks to the University of Nottingham for granting me the permission, support and resources as part of my PhD program.

7. Chapter VII- Conclusions

This final chapter will draw together some of the issues raised and original lessons gleaned by other parts of this body of work.

7.1 Introduction (Chapter I)

Although the *causes* and association of aggression are multiple and complex, there is good evidence that its prevalence in psychiatric settings is high but that treatment approaches have considerable variance worldwide. The initial scrutiny of the prevalent and authoritative literature in this field still warrants careful re-consideration by interested students and can yield original, novel, results.

Additionally, chapter I explores the important framework, literature and the evolution of management in the psychiatric emergency setting including prevention, de-escalation measures and active management as well as policy and practice pertaining to rapid tranquilisation citing similarities, differences and unique measures internationally, nationally and locally.

7.2 Finding and summarising surveys (Chapter II)

Chapter II was a systematic review of surveys. This was seen as a prerequisite to a Lebanese survey. Although a diversion from the core purpose of this thesis, the investigation into the

systematic searching for this ostensibly simple, but bedrock methodology – the survey – proved informative. Many research projects start with some form of survey and, in turn, it is important to be sure that some foreknowledge of scope and design of others' work is acquired. The researcher can lose much time and enthusiasm in searching in a way that is felt to be far from systematic. The original work at the start of Chapter II provides the researcher with both good and bad news:

- Being systematic in finding surveys is, currently – at best very problematic – at worst impossible.
- Searches are likely to yield results about which it is impossible to be fully confident that they represent an unbiased sample of the total 'population' of studies.
- Authors and editors could greatly improve citation of their work by inclusion of the methodological description (e.g. 'survey') in the titles.

The 21 surveys that were identified were of variable quality and size. Although there is a broad consistency in pharmacological approach – with use of antipsychotic drugs or benzodiazepines – the variation of choice is considerable – and what has been found – repeatedly - is that what happens in practice does not necessarily reflect what is recommended or

thought to happen by opinion leaders. The surveys identified did point to variation of approach by region and I found no survey of practice or opinion in the Middle East. This encouraged the need for one and the surveys identified – both good and bad – did help inform design of the Beirut survey of Chapter III. Without this overview the reinvention of methods would have been more difficult. I learnt that any survey is difficult to undertake well, that larger and longer does not necessarily mean more informative and that simple can suffice.

I found further encouragement in surprising places. The large UK-based POMH-UK 'survey' (POMH-UK, 2017) – by far the largest 'survey'[5] of its kind – reported some evidence of a change in what seemed to be entrenched national UK practice (as highlighted in UK-based surveys predating POMH-UK) in what seemed to be a reaction to new evidence and guidance. Practice can change – improve - over time, and evidence and good guidance may have a part to play in that.

7.3 New survey in one large hospital in Beirut (Chapter III)

An evaluative study of the effects of treatments used in everyday care can only be undertaken if:

[5] Parenthesis denote that this was not really a survey but, really, a very large case series.

- The routine treatments are known,
- There is an evidence-gap regarding those treatments, and
- There is a large consensus for an evaluative study to happen.

The Beirut survey of emergency treatment was imperfect – mainly due to clinicians being avoidant and reluctant in filling out the opinion questionnaire. However, it did clarify routine practice – and begin to predict recruitment for a potential evaluative study. By its conduct, the survey also laid foundations for the design of the future trial. Front line health care professionals began to realise that this student was truly interested in everyday care – and this student began to realise the enormously difficult job the health care professionals undertook every day of the week, every hour of the day. [Around this point, the student also had realisation of the difficulty of evaluation of this point of care.]

The survey also found, that, in keeping with other work from across the globe, that what clinicians hope is undertaken in the emergency room is not necessarily what happens. The opinion of what should be used, or their order of use did not fit with the reality of clinical care. In this, Lebanon is the same as

other places. Also, the experienced clinicians of Lebanon, like the UK, the USA and many other places, are routinely using effective treatments robust for managing individuals at risk of an aggressive episode. In this case, it includes a less common combination of haloperidol plus promethazine plus chlorpromazine - seen previously only in Brazil. So, Lebanon was distinct but also had similarities probably arising from the clinical necessity of management, the limited trusted choices and traditions of care.

It remained unclear if Lebanon was similar to other countries such as the US and UK – in that it was treating people without their consent with potent treatments but untested in randomised clinical trials. This led to the search for evidence from high-grade evaluative studies.

7.4 Overviewing effects of treatments relevant to Lebanon (Chapter IV)

Chapter IV was a systematic review of systematic reviews – an overview. The methods for undertaking overviews are evolving (Higgins et al., 2019) and I tried to keep focused on the treatments relevant to Lebanese practice, and to identify systematic reviews in a systematic manner. Where these systematic reviews were potentially out of date, I endeavoured to find any new relevant trials – again by use of searches that

could be described and, if needs be, repeated. Being less than systematic is not difficult but undermines confidence in the findings. Being as systematic as possible currently pushes review methodology boundaries and is difficult – but gives some confidence in the result.

Overall, the *quality* of evidence relevant to treatments in everyday use in Lebanon is variable. Quality ratings of the key outcomes of interest range from non-existent through 'very low' (the commonest grading) to 'high' (once). A key issue was that the highest quality evidence is for an intervention that is available and acceptable in Lebanon (haloperidol + promethazine) and that these data are from randomised trials undertaken in similar health care traditions. Pragmatic trials in low-middle income country conditions were possible, informative and influential.

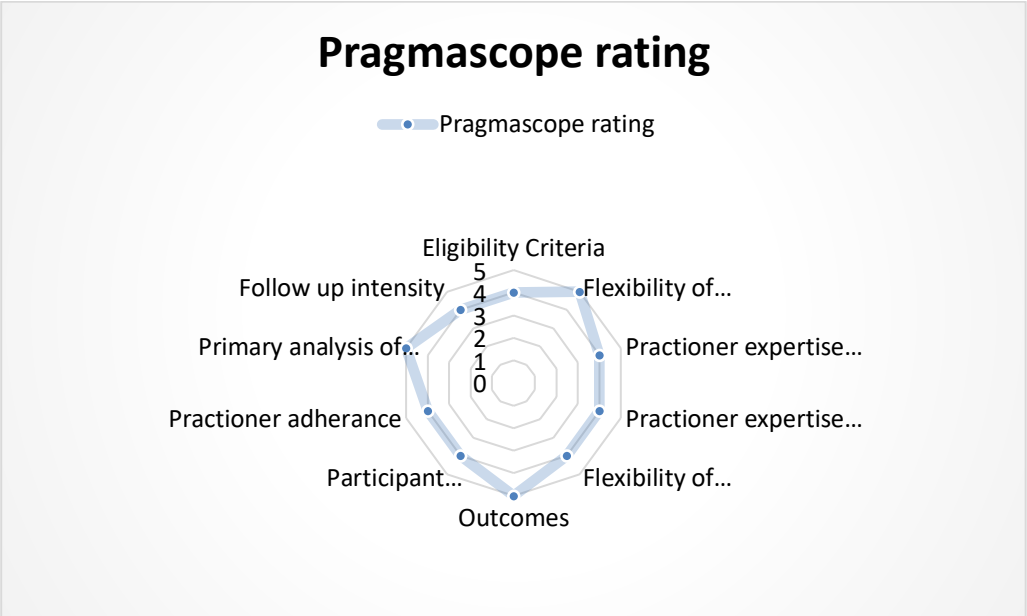
A second key issue was that I identified no systematic review, no un-systematic review and no randomised trial of the most common drug intervention package used in Lebanon (the haloperidol, promethazine, chlorpromazine combination). The triple combination clearly worked and had been tested by long use at the clinical front line. It had not, however, been tested in a randomised trial. The latter affords opportunity to quantify effects and to fairly test against a worthy competitor – and the

much better-tested haloperidol plus promethazine mix was just that.

7.5 The TREC-Lebanon protocol (Chapter V)

While following the same pragmatic design as past TREC trials, the TREC-Lebanon protocol was adapted to Lebanese tastes and practice. Meetings were held; clinicians were consulted. The process of consultation was two sided. Compromises of design had to arrive at, and this meant 'give' on both sides. Well-resourced trials can employ dedicated staff and even establish services in which the trial takes place. Many outcomes of value to *research* can be gleaned as well as clinically meaningful results. For less well-resourced studies, however, simplicity of design is key, and the target readership is important. For TREC-Lebanon, clinicians were the targets. The views of this group on what outcomes were important and how to arrive at these was key. I would have liked more consultation. In retrospect the design – admirably pragmatic (see Figure 7.1: Pragmascope– could, nevertheless, have been improved upon (Tosh, Soares-Weiser, & Adams, 2011).

Figure 7.1: Pragmascope



The major outcomes that were acceptable to the clinicians were similar to those of other studies. In accepting these, it was anticipated that the findings could eventually be compared with others across the globe. This was found to be true.

However, one aspect of design that I found could not be emulated in Lebanon was 'Dr Stopwatch'. The Brazilian and Indian TREC trials had one additional timing check – a medical student with a stopwatch to surreptitiously time the period between injection and tranquillity. This served to cross-validate nurse's estimates of tranquil/calm at the designated times. In the Brazilian and Indian trials, the estimates of period to tranquillity did tally closely with the surreptitious stopwatch timings. In TREC-Lebanon, because of so few staff

being available this technique could not be used. Residents were asked to start the timer on their telephone and note, on an additional form, a 'true tranquilisation' time – not one constrained by the 20, 40, 60, 120-minute boxes. In this way, if the aggression/disturbance passed the 2 hour interval, the resident could note the time the patient did eventually become tranquil or asleep. This does not represent independent validation and is a weakness in TREC-Lebanon's design. What evidence there is from the other TREC studies is that the categorical estimate of time to tranquillity is good but the absence of internal validation within TREC-Lebanon is a design problem that it would have been better to avoid.

That Lebanon does not use emergency rooms, preferred 'mobile' envelopes to 'static' boxes, involved primarily the residents and less the nurses did not seem insurmountable issues. The protocol was adapted to Lebanese needs and was registered (See https://clinicaltrials.gov/ct2/show/NCT03639558?cond=TREC&rank=2) and published (Dib et al., 2019). Further difficulties in the trial design – and subsequent conduct – only became apparent once the study was running and so are highlighted below.

7.6 The trial - TREC-Lebanon (Chapter VI)

7.6.1 Ethics

A number of dilemmas arose before and during TREC-Lebanon in areas concerning ethics. Initially, TREC-Lebanon was scheduled to commence six months before its actual start date but a number of unforeseen circumstances relating to ethics ultimately lead to trial commencement being stalled until both parties (Nottingham and Psychiatric Hospital of the Cross) were satisfied with a mutual agreement. I think these problems are important and some are specific to TREC-Lebanon and would benefit from discussion.

a. General ethics

TREC-Lebanon was a pragmatic patient randomised trial evaluating two combinations of medication for the treatment of acute agitation in psychiatric patients. Both combinations of medication are used routinely in medical practice in Lebanon. The study did not obtain informed consent from participants, but it did from next of kin, should they have been present. Study participants were certainly vulnerable persons because (1) they were incapable of providing informed consent and (2) they are suffering from an acute mental illness - or intoxication. Participants were vulnerable also, outside the context of a trial, to receive, in good faith, treatments not

rigorously tested to the highest standards. In everyday care the vulnerable are being given treatments tested by long service, observation and tradition, rather than best science. There is a difficult balance to strike. The International Community of Medical Journal Editors (2008) requires that "All investigators should ensure that the planning conduct and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013.". If the study does not follow the Declaration of Helsinki in some regard, "the authors must explain the rationale for their approach and demonstrate that the local, regional, or national review body explicitly approved the doubtful aspects of the study.”.

I am grateful to Professor Charles Weijer (Professor in the Departments of Philosophy and Medicine, and Canada Research Chair in Bioethics at Western University in London, Canada) for helping me clarify my thought on these difficult issues and, consequently, helping with the clarification of the protocol and the conduct of the trial.

Table 7.1: Declaration of Helsinki ethics

Declaration of Helsinki statement		**How addressed in trial**
Paragraph 25	Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.	TREC-Lebanon provides both an Informed Consent and Patient Consent form (See Chapter V: Protocol, Section Triage to Randomisation).
Paragraph 28	Patients who are unable to provide informed consent must have a legally authorised individual to do so.	In TREC-Lebanon, family members of legal guardian fit this parameter (See Chapter V: Protocol, Section Triage to Randomisation
Paragraph 30	Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.	For inclusion in TREC-Lebanon patients were in (1) an aggressive state and not mentally competent to understand and sign an informed consent and/or (2) have a psychiatric condition that also renders them mentally incompetent of comprehending and signing an informed consent which are stated in Chapter V: Protocol, section Ethical Rights and Consent. The Ethics Application file provided by the Lebanese Hospital of the Cross (See Supplementary File: Ethics Application) included the background of the study citing TREC-Lebanon is a non-consenting trial due to the nature of condition of patients involved (see above) and patients are unable to consent. However, consent to remain in the trial (See Supplementary File: Consent form) was given to all patients post randomisation in accordance DoH Paragraph 30.

TREC-Lebanon did involve randomisation of potent treatments of vulnerable people who – by the very inclusion criteria of the trial – could not give informed consent. The Declaration of Helsinki overtly and rigorously defends the rights of this group of people but also, by its rigour, the rights of ethical researchers to investigate in order to make care better and more based on evidence. TREC-Lebanon did attempt to walk that line and, I argue, succeeded in doing so. Part of the argument was the covert vulnerability of patients and clinicians in receiving or giving routine practice. For example, in the UK tradition of routine treatment haloperidol IM is commonly used, without patient consent, for management of acute aggression (POMH-UK, 2017). This is despite the clear evidence of accessible and better treatments (POMH-UK, 2017). Indeed the largest relevant trial involving one treatment arm of IM haloperidol was stopped early by the Steering Group as it was felt unethical to continue to deliver this treatment (Huf et al., 2007). The overt guidance of the Declaration of Helsinki along with the covert contradictions of every day practice does make a strong argument – but logistical problems were still to cause problems to the smooth passage of TREC-Lebanon.

b. Logistical issues

Of course, randomised clinical trials (RCTs) require ethical approval (Nardini, 2014) and TREC-Lebanon, which was part of a PhD program, required ethical approval from *two* bodies. The first was the University of Nottingham where the PhD program I was based and the second, The Psychiatric Hospital of the Cross, where the [survey and] trial was to be undertaken.

The University of Nottingham has two ethics committee. First, the program is part of the School of Medicine - specifically the Division of Psychiatry and Applied Psychology (DPAP). As a result, the two ethics committees are:

- Divisional Ethics - that includes applications specifically within the school's division.
- University Ethics - that, if the Division Ethics Committee sees the application is beyond the division's scope, will forward it to the University Ethics Committee.

The Division of Psychiatry and Applied Psychology Research Ethics has three steps for all projects requiring ethical approval which include discussion, submission of application and the review process. Guidance for students and supervisors is available to download and this is updated to be sufficient and suitable for all student projects. Within the guidance,

Heading 6 of 'Making an application' is the subsection 'Organisational permissions or external ethical review'. It states:

> *'Students undertaking projects in outside organisations need to provide evidence (an email or headed letter) that the project has been approved by a suitably authorised person from that organisation. This may not be available at the time of application for ethical review. In which case, supervisors will undertake to check such permissions are in place before they permit the student to begin approaching potential participants. Supervisors should check that the letter of organisational permission accurately reflects the proposed study. If the study is to be conducted in an outside organisation it also needs to be established whether that organisation has its own ethical scrutiny procedures.'*

The survey of clinicians' opinions and practices (Chapter III) required ethical consent since it required surveying treatment practices given to patients. As the survey was undertaken in Lebanon, the application had an attached form indicating the Ethics Committee of the hospital in Beirut granted approval for the survey to be done. The application was sent to the School Division and was given ethical approval one month later. This passage of ethics proved a useful template for the trial itself.

As for the TREC-Lebanon trial, another application was created noting that the trial was to be conducted outside the UK. However, the School Division Ethics committee advised that, because of the nature of the trial, it should be sent to the University Ethics Committee. I presume that this was an issue of being "beyond the Division's scope". However, upon sending it on, the University Ethics Committee replied indicating that it is best suited for the School's Divisional Ethics Committee to review the application. An application was formally made on October 10th, 2017 but the stagnation and the back and forth process continued until August 2018 with a final agreement that the proposed project does not require ethical approval from their part – in accordance with heading 6 of the guideline stated above. All data entering the UK was to be fully anonymous but as the trial was being undertaken in Lebanon, and this had passed the local ethics committee, approval for *the trial* not was required in the UK whilst its analysis was – and was granted.

I recognise that TREC-Lebanon is particularly delicate. It is a randomised trial. It was evaluating a treatment untested in trials before for people who just cannot give consent. TREC-Lebanon also ran across two jurisdictions. However, in the UK there was the impression that it was not clear where responsibility really lay as regards ethics and the subsequent

ping-pong of submission was unhelpful to the research. The survey methods were relatively easily approved by the Divisional Committee, but the randomised trial, with its much more uncomfortable responsibilities, was batted between the two committees. For future students, it would be helpful if the university guidance is updated and made very clear.

With research running across different countries, of course, there is the risk of one country judging the others ethical standards from some privileged or even righteous standpoint. There is, of course, need for *judicious* use of judgement, across countries, albeit with the danger of criticism. With TREC-Lebanon there was no real issue of privilege or righteousness. Although the UK's health service is massively better funded than the Lebanese system, the UK and Lebanon stand on level ground as regards randomised research in this area. There is none. The UK, like Lebanon, uses indirect data undertaken in other countries for its national guidance (National Collaborating Centre for Mental Health, 2015). Indeed, it would seem unlikely that trials used in the UK's guidance (Wright et al., 2001) would pass through the ethics committees of the UK – or, for that matter, Lebanon. Furthermore, there is little place for righteousness. In both countries thoughtful, careful and caring clinicians try to treat people as best as is possible but from outside the scientific

security of best evidence from trials – leading to diverse practice, even within each country. However, just because both jurisdictions are less than perfect did not necessary mean it was right to undertake TREC-Lebanon. I continue to attest that it was, and have tried to base argument on common sense and humane logic, supported by trans-national declarations on ethics.

7.6.2 Design

a. Feasibility

The short feasibility phase of the trial involving only five patients was invaluable. It helped the residents accommodate to the trial procedures, smooth out some logistical issues at the very start (it was better to have envelopes in resident's pockets rather that in the research officer's room) and it helped me gain confidence in the ability to undertake this part of the research. A longer feasibility phase was precluded by the urgency of commencement of randomisation but probably would have benefited TREC-Lebanon more. It would soon have become obvious that the adverse event form, although agreed upon, was not being used and that the 'doctor called' outcome should have been 'doctor called *back*' to capture a measure of recurrence of the aggression of the index episode.

b. Adverse events

A simple adverse events form was agreed upon and designed into the trial. It is well known that antipsychotic medications do pose a risk of adverse effects. But the study recorded no adverse effects from the allocated medications. I inquired specifically about this lack of recorded adverse effects (such as the expected extrapyramidal effects) at the 50th patient mark – and, later, upon trial completion. The clinicians assured me no adverse effects occurred yet the indirect evidence of use of the anticholinergic trihexyphenidyl suggests there were, at least, some. In a more explanatory trial extra care – perhaps an extra person with a checklist observing every trial entry – would probably have highlighted more adverse effects. In this pragmatic study, however, any extrapyramidal effects were not seen as problematic – at least by the clinicians. In designing and conducting trials there has to be much striking of balances. I am not sure if I struck the perfect balance of data acquisition. Of course, available [shoestring] resource had to be taken into account – but this was only one factor. Clipboard observation is outside of routine care. There was a real danger that the rigorous pursuit of outcomes that are just not deemed that important in this situation in Lebanon would have alienated clinicians – and then the perfect would have been the enemy of the good.

c. Doctor called

As stated above, not clarifying that recording that the doctor was called *back* was a mistake and I did not realise that these data were impossible to attain from the case files.

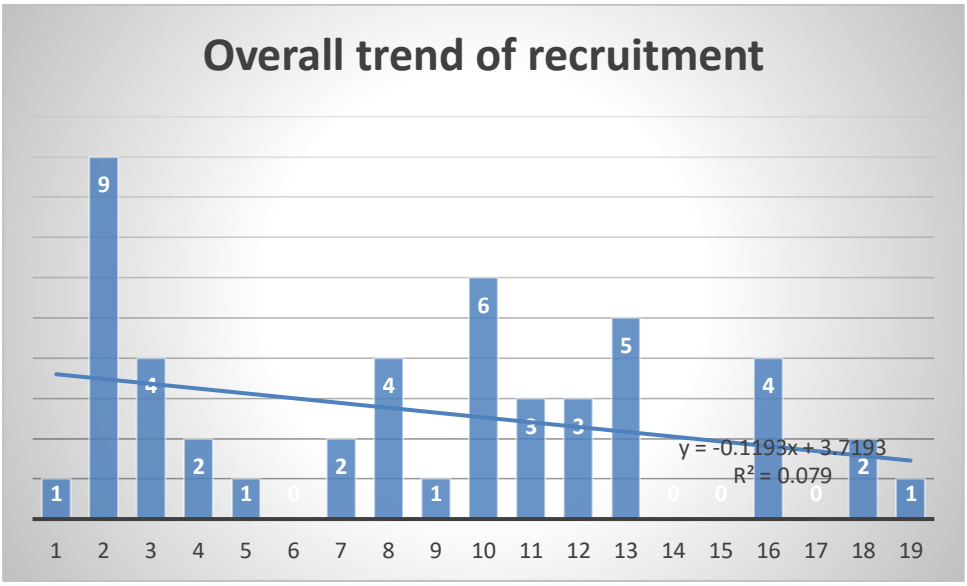
7.6.3 Conduct

As the trial progressed, certain issues arising from routine care became apparent which, in retrospect and for future work, could, to some extent, be considered and the problems offset.

a. Residents' turnover

The residents of the Psychiatric Hospital of the Cross helped design and then run the trial. However, residents involved within the hospital are not on permanent contract and would leave. Moreover, not all residents in the hospital were interested in taking part. This posed two problems. Firstly, new incoming residents had no ownership of the study. Second, recruitment opportunities had to be missed if a resident who was not interested in the trial was on duty.

Figure 7.2: Recruitment rate (Weeks)



TREC-Lebanon recruitment was really in two phases. The first (patient 1-48) was undertaken by four residents (Werner, Tony, Elie and Hiba). The second (patient 49-100) involved five residents (Maria, Marc, Jean Mark, Hiba and Myriam). Only Hiba stayed for the whole study. The four new residents had to be trained and thereafter the pace of recruitment increased.

b. Espirit de corps

Closely related to this issue of ownership is that of *esprit de corps*. Good will goes a long way but has to be maintained and not abused. All residents will have their name on a final paper of the trial. WhatsApp supported and encouraged. Periodic visits by myself did, I think, boost interest in the trial and subsequent recruitment. How often to undertake a 'site visit'

and what is the best encouragement for involvement remains likely to be a matter of judgement – and resource.

c. Two and a half nurses

Unlike the other TREC studies, TREC-Lebanon had more of a division between nurses and residents. It had been hoped that TREC-Lebanon involved all members of hospital staff in design - just as they would during a real emergency episode. However, the senior clinicians felt that they could trust the input of the resident doctors more than that of the nurses. The latter were felt to be less experienced in 'research understanding' and there was the feeling that nurse input could pose a risk to the trial procedure. The nurses, for their part, also mentioned that their workload was already distressing and that they did not want to take on what they saw as additional work.

Certainly, the hospital is severely understaffed. TREC-Lebanon was simple and not intrusive. It did not require heavy human resources in order to run. There was, however, little choice in the design of the trial. Nursing input could have improved TREC-Lebanon and it would be hoped that seeing this opportunity, nurses of the future could feel more empowered to take a more active role next time – and doctors could also see the great value in this.

d. Sister Margaret's gone to church

The hospital's sisters work as librarians and in administration. Originally, they were to be part of the 'Dr Stopwatch' team (See Chapter V) which meant they would surreptitiously fill out the Dr Stopwatch form unbeknownst to residents and nurses. There did seem to be a willingness for this to happen, but I did find some evidence for the doctor's accusation of there being little 'research understanding' and input was unreliable. Perhaps a longer test phase would have given the sisters an opportunity to develop skills and show the attending doctors that they did have the ability and understanding to take part in the study.

e. Emergency room availability

Although the survey did reveal that an emergency room was not present in this hospital and the trial ran - the lack of such a room did probably affect survey numbers and, perhaps, trial recruitment. For instance, when agitated patients are brought to the hospital for the first time, they are registered in the administration centre and are swiftly moved on to their designated ward. Nurses describe how many patients are agitated and aggressive before being escorted to the ward but become calm when placed in their room on the ward. The exact opposite also happens. Initially patients may be calm but

exhibit a violent episode when escorted to their ward. It was really this latter group that were randomised into TREC-Lebanon. The survey could not record how many patients exhibited a violent episode in the administration centre before being transported to the ward.

This small observation poses many testable questions. Would provision of a safe space as early as possible in the procedure prevent aggressive episodes? Could changing of approaches either at the administration or on the ward modify outcome? Is time spent in company of family/law enforcement personnel helpful or not? Much to do with the care of this vulnerable group is not researched and could be. This thesis focuses on only one aspect of a complex set of interactions.

f. Funding

All TREC-Lebanon's funding was intramural. Participating residents and nurses did not receive funding. There are advantages to running trials on minimal funds (Lede, 1999) but it is not easy. Some more support would have helped, at the very least, *espirit de corps*, and, therefore, probably recruitment. Most residents wanted the trial to run and the nurses, at least, gave tacit approval to its conduct. Funding to help with training, team building, paying for that much-needed cupboard, or coffee machine could have been useful. Good will

does go a great distance and is present even in the very constrained circumstances of middle-income country front line care. Doing something good that even the mighty powerhouses of research such as the UK, USA and even Israel, have failed to do does help motivation – but I also think nicely brewed coffee would also have helped.

7.7 Where from here?

7.7.1 The results

The haloperidol plus promethazine mix is now the most widely researched drug treatment for people with aggression thought due to psychotic illnesses. In the small trial of TREC-Lebanon there was no indication that this combinations (HP) ability to swiftly make the situation calm were different to that of a more complicated drug mix (HPC). There is an argument that, where both the double and triple therapy options are used, and it is unclear which is really indicated in the particular clinical situation, that the HP mix should be prescribed in preference. I hope, in the company of the staff of the hospital, to write these findings up for wide publication and, by doing so, impact on policy.

7.7.2 Future of clinical trials looking at rapid tranquilisation in the psychiatric setting

We know that, in psychiatric emergencies:

- Treatment variation is considerable – locally and nationally;
- Surveys of treatment opinions differ with surveys of practice; and
- High profile guidelines give recommendations that can be contradictory.

Further research is really needed. These problems are not limited by region and they apply to all centres where emergency psychiatry takes place. Countries with a high-income status (i.e. UK, USA, etc.) to countries with middle to low income status (such as Lebanon) do all require evidence derived from randomised trials. That TREC-Lebanon could be completed is proof that such studies are possible in countries that lack substantial funding. It is no one jurisdiction's responsibility to provide research evidence for the rest of the world. Everyone working in clinical care can question and enquire and be curious about existing evidence.

Pragmatic trials are uncommon in psychiatry but are recognised as a potent source of real-world evidence (Zwarenstein et al., 2008). They are more possible in low-middle income country situations than explanatory work and are likely to provide more useful, clinically meaningful, data. This does not mean they are easy to conduct, analyse or report and that standards are not as high as for other studies

(please see Appendix L). Interested researchers can help design and run these trials almost anywhere, with the resulting impact worldwide and into front line care. Clinical trials from the Middle East and North Africa are rare (Nair, Ibrahim, & Celentano, 2013) but not impossible. The population across this region rivals that of North America but the research output does not. Gross Domestic Product (GDP) is certainly a potent stimulus to trials (Glick, Doshi, Sonnad, & Polsky, 2014) but so is curiosity, energy and the confidence generated by vanguard trials.

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7.9 References

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8. Appendices

Appendix A: Tables of Index Terms

Table A1: MEDLINE index terms

Methodology	Generic		Refined	
	#1	Clinical Protocols/ OR Research Design/ OR "Surveys AND Questionnaires"/ OR Pilot Projects/ OR Patient care management/ OR Drug administration schedule/ OR (Frequently OR Inciden$ OR Management OR Medical Practice OR Practices OR Prevalence OR Prospective OR Questionnaire OR Structured Interview OR Survey$).ti,ab. OR (Current Practices OR Manag* OR Contemporary).ti.	#1	Patient Care Management/ OR (Inciden$ OR Survey$).ti,ab.
	Results			
	3,600,597		1,200,084	
Aggression	Generic		Refined	
	#2	Aggression/ OR Antipsychotic Agents/ OR Antipsychotic Agents/ OR Dangerous Behavior/ OR Drug Protocols/ OR Drug Utilisation/ OR "Emergency Service, Hospital"/ OR Emergency Services/ OR "Hospitals, Psychiatric"/ OR "Injections, Intravenous"/ OR Mental disorders/ OR Patient Compliance/ OR Restraint/ OR Violence/ OR "Violence prevention AND control"/ OR (Aggravat$ OR Aggress$ OR Behavioural Disturbances OR Rapid Tranquilisation OR Resisting OR Restrain$ OR Sedation OR Violen$).ti,ab. OR (Agitation OR Disturbed).ti.	#2	Aggression: Aggression/ OR Violen$.ti,ab.
	Results			
	710,553		46,427	
Combined Search	Generic		Refined	
	#3	#1 AND #2	#3	#1 AND #2
	Results			
	194,765		**8,822**	

Table A2: EMBASE index terms

Methodology	Generic		Refined	
	#1	Case Management/ or Clinical Practice/ or Clinical Protocol/ or Clinical Study/ or Controlled Study/ or evaluation/ or prevalence/ or health survey/ or incidence/ or major clinical study/ or medical practice/ or mental hospital/ or patient care/ or (Current Practices or Contemporary or Frequently or Inciden$ or Manag$ or Medical Practice or Practices or Prevalence or Prospective or Questionnaire or Structured Interview or Survey$).ti,ab.	#1	Incidence/ or (Inciden$ or Manag$).ti,ab
	Results			
	10,816,529		2,365,166	
Aggression	Generic		Refined	
	#2	Affective neurosis/ or aggression/ or Agitation/ or controlled study/ or drug efficacy/ or drug mixture/ or drug safety/ or drug therapy/ or Emergency health services/ or Emergency ward/ or intramuscular drug/ or administration/ or intravenous drug/ or administration/ or major clinical study/ or mental hospital/ or oral drug administration/ or Restraint/ or Sedation/ or Tranquilizing activity/ or Violence/ or (Aggravat$ or Aggress$ or Agitat$ or Behavioural Disturbances or Disturbed or Rapid Tranquilisation or Resisting or Restrain* or Sedation or Violen$).ti,ab.	#2	(Behavioural Disturbances or Disturbed or Restrain* or Violen$).ti,ab.
	Results			
	8,663,984		143,610	
Combined Search	Generic		Refined	
	#3	#1 AND #2	#3	#1 AND #2
	Results			
	7,501,929		**14,964**	

Table A3: PsychINFO index terms

Methodology	Generic		Refined	
	#1	Case Management/ or Pilot Projects/ or Epidemiology/ or Management/ or "Surveys and Questionnaires"/ or (Current Practices or Contemporary or Frequently or Inciden$ or Manag$ or Medical Practice or Practices or Prevalence or Prospective or Questionnaire or Structured Interview or Survey$).ti,ab.	#1	(Inciden$ or Manag$ or survey$).ti,ab.
	Results			
	953,434		517,376	
Aggression	Generic		Refined	
	#2	Aggression/ or Aggressive Behavior/ or Antipsychotic Agents/ or Dangerous Behavior/ or Injections,Intravenous/ or Patient Compliance/ or Patient Violence/ or Psychiatric Hospital Staff/ or Psychiatric Hospitals/ or Psychosis/ or Violence/ or (Aggravat$ or Aggress$ or Agitat$ or Behavioural Disturbances or Disturbed or Rapid Tranquili?ation or Resisting or Restrain* or Sedation or Violen$).ti,ab.	#2	(Rapid Tranquili?ation or Restrain$ or Violen$).ti,ab.
	Results			
	208,912		85,812	
Combined Search	Generic		Refined	
	#3	#1 AND #2	#3	#1 AND #2
	Results			
	58,270		**16,038**	

	Region (sorted #1)	Africa	Americas				Australia		Europe													
	Country (sorted #2)	5 countries	Brazil	Canada	USA	USA	Australia	Australia	Belgium	France	Ireland	UK	UK	UK	UK	UK	UK	UK	UK	UK	UK	21 countries
	Date (sorted #3)	**2011**	2002	1986	1998	2014	2001	2011	2015	1999	1997	1983	1992	1994	1996	1996	2003	2006	2006	2012	2017	2003
	Author	**Bawo**	**Huf**	**Rapp**	**Binder**	**Allen**	**Cannon**	**Chan**	**Bervoets**	**Moritz**	**Mannion**	**Cooper**	**Pilowski**	**Cunnane**	**Thacker**	**Simpson**	**Reid**	**Antwi**	**Pereira**	**Haw**	**POMH**	**Lepping**
	Target	Clinicians	Patients	Patients	Clinicians	Clinicians/ Patients	Clinicians	Clinicians/ Patients	Clinicians	Patients	Clinicians	Patients	Patients	Clinicians	Clinicians	Clinicians	Clinicians	Clinicians	Clinicians	Patients	Clinicians/ Patients	Clinicians
	Duration	N/A	1 /52	1/12	1/12	N/A	4/52	4/12	3/12	9/12	6/12	6/12	5/12	N/A	N/A	2/12	N/A	N/A	N/A	N/A	1 year	N/A
	Contact	Online Survey	Interview	Interview	Telephone	E-Mail	E-Mail	E-Mail	Online Survey	Interview	Interview	Interview	Interview		N/A	E-Mail	E-Mail	Telephone	E-Mail	Interview	Interview	Interview
	SSQ		✓		✓			Case vignette					RTQ	Clinical vignette	Case vignette							
	N	42	74/74	12	20/20	`	79/116	786/2052	108/550	100	55/65	34	60/60	28/50	30/78	69/100	180/215	66	257/582	316	2172	N/A
	Sex	N/A	N/A	M:9 F:3	N/A	N/A	N/A	N/A	M:69 F:39	M:57 F:43	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	M:195 F:121	M:1196 F:976	N/A
	Age	N/A	N/A	Median: 27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Median: 36	N/A
	Diagnosis	N/A	N/A	S:7, M:2,PD:3	N/A	N/A	32% P 10% ABS	N/A	N/A	SU: 73%, P: 22%	N/A	S:20, D:2, M:7,PD:3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Quality % (Table 5)	66%	87%	58%	62%	70%	75%	83%	83%	79%	62%	66%	83%	54%	66%	75%	62%	62%	45%	62%	70%	
Antipsychotic	Aripiprazole (A-A)								3												76	
	Chlorpromazine (A-C)	0	1%	14						14	26	✓	#3	14	✓	✓	✓				8	
	Clotiapine (A-CL)								17													
	Cyamemazine (A-CY)									5												
	Droperidol (A-D)				4	✓			5	5	18		#4	1	✓	✓	✓					
	Haloperidol (A-H)	18		16			93%	5,80%	3	15	26		#2	8	✓	✓			✓	25	613	#1
	Loxapine (A-L)									67												
	Olanzapine (A-O)							4,90%	17								✓			21	75	
	Promethazine (A-P)																			1		
	Promazine (A-Pr)		**1%**																		11	
	Pipamperone (A-Pi)								3													
	Risperidone (A-R)																				16	
	Sultopride (A-S)									7												
	Quetiapine (A-Q)								5													
	Zuclopenthixol (A-Z)	2							2		45				✓		✓			4	67	#2
	Unspecified (A-U)													1								

		Africa	Americas				Australia		Europe													
	Country (sorted #2)	5 countries	Brazil	Canada	USA	USA	Australia	Australia	Belgium	France	Ireland	UK	UK	UK	UK	UK	UK	UK	UK	UK	UK	21 countries
	Date (sorted #3)	**2011**	2002	1986	1998	2014	2001	2011	2015	1999	1997	1983	1992	1994	1996	1996	2003	2006	2006	2012	2017	2003
	Author	**Bawo**	**Huf**	**Rapp**	**Binder**	**Allen**	**Cannon**	**Chan**	**Bervoets**	**Moritz**	**Mannion**	**Cooper**	**Pilowski**	**Cunnane**	**Thacker**	**Simpson**	**Reid**	**Antwi**	**Pereira**	**Haw**	**POMH**	**Lepping**
	Amobarbital (B-A)										2											
	Alprazolam (B-Al)								5													
	Bromazepam (B-B)								1													
	Clorazepate (B-C)								9	5												
	Chlordiazepoxide (B-Ch)									2												
	Clonazepam (B-Cl)		**9%**																		50	
	Diazepam (B-D)	38				✓	59%			7	6				✓	✓					44	
	Lorazepam (B-L)	2							14		32				✓	✓			✓	108	652	#1
	Meprobamate (B-M)						82%			7												
	Midazolam (B-Mi)							79,40%													8	
	Prazepam (B-P)								1													
	Unspecified (B-U)				3								#1									
Combinations	A-H + B-L +/- 1*				13	✓								1						44		
	A-H + 1				1																	
	A-D + B-L + 2*				1																	
	A-C + A-H													2								
	A-H + B-D		**1%**											1								
	A-H + A-Pr		**61%**																			
	A-H + A-pr + BD		**15%**																			
	A-H + A-Pr + A-C		**7%**																			
	Manual				14	✓	87%			86%												
	Seclusion					✓	23%															
Delivery	IV				2	✓					3		50%	2	✓					203		
	IM		74		15	✓				✓	7		50%*	16	✓						n=1079	
	Oral										4										n=1236	

* Anticholinergic drug; 1 – Benztropine, 2- Diphenhydramine

Appendix C: Survey Forms

Form C1: Clinicians' Form

Name: …… Role: ……..

Ward: …… Period of work in mental health: ……

QUESTION: How often would you have to manage a person who is acutely aggressive?

QUESTION: When someone is acutely aggressive - what do you think should be used to manage this?

*Note: Feel free to fill out the intervention steps based on the idea if previous intervention was not successful.

Intervention #1:……

Intervention #2:……

Intervention #3:……

Intervention #4:……

Intervention #5:……

Intervention #6:……

Intervention #7:……

Intervention #8:……

Intervention #9:……

Would you like to see the results of this survey? Yes ☐ No ☐

Form C2: Emergency Management Form

Unique ID:		Ward:	
Suspected cause:		Diagnosis (if applicable):	
Date:	Time:	Age:	Sex:
Presentation: a- Family b- Authorities c- Friends d- Self e- Other			
Restraints before admission: Y/N	If yes, what type of restraint and what duration [if possible]:		
Given treatment before admission? Y/N	If YES – what was he/she given? **(directly given by professionals)**		
	If YES – what was he/she given? **(directly given by family/carer/self)**		

Medication after admission for this episode [name, dose, route]:

Medication #1:	
Medication #2:	
Medication #3:	
Medication #4:	
Medication #5:	
Medication #6:	
Medication #7:	PTO if necessary

Appendix D: Individual episode data for emergency medication (IM)

	ID	Medication1	Medication2	Medication3	Medication4	Medication5	Medication6
1	25834	Diazepam	Haloperidol + Promethazine				
2	29834	Haloperidol + Promethazine					
3	26502	Strait Jacket	Diazepam	Haloperidol + Promethazine + Chlorpromazine	Haloperidol + Promethazine + Chlorpromazine	Zuclopenthixol + Promethazine	
4	33666	Diazepam	Chlorpromazine				
5	33810	Diazepam					
6	34695	Diazepam	Lorazepam				
7	37681	Haloperidol + Promethazine+Chlorpromazine	Chlorpromazine	Diazepam			
8	37692	Chlorpromazine	Haloperidol +Promethazine +Chlorpromazine				
9	38166	Verbal Command	Strait Jacket	Haloperidol + Promethazine + Chlorpromazine	Promethazine	Chlorpromazine	
10	39672	Haloperidol + Promethazine + Chlorpromazine					
11	39672	Haloperidol + Benzhexol + Promethazine					
12	39672	Chlorpromazine + Lorazepam					
13	39672	Chlorpromazine + Lorazepam					
14	40059	Haloperidol + Promethazine + Chlorpromazine	Lorazepam				
15	41721	Strait Jacket	Haloperidol + Promethazine + Chlorpromazine	Diazepam	Chlorpromazine	Promethazine	
16	41967	Diazepam					
17	41967	Zuclopenthixol + Promethazine					
18	41967	Zuclopenthixol + Promethazine					

	ID	Medication1	Medication2	Medication3	Medication4	Medication5	Medication6
19	42945	Haloperidol + Promethazine + Chlorpromazine	Diazepam				
20	42945	Haloperidol + Promethazine + Chlorpromazine					
21	42945	Haloperidol + Promethazine + Chlorpromazine	Diazepam				
22	42952	Strait Jacket	Haloperidol + Promethazine + Chlorpromazine	Chlorpromazine	Promethazine		
23	43695	Haloperidol + Promethazine	Haloperidol + Promethazine + Strait Jacket				
24	43877	Haloperidol	Chlorpromazine	Benzhexol			
25	44328	Haloperidol + Promethazine + Chlorpromazine + Lorazepam	Clozapine	Benzhexol	Promethazine	Promethazine	
26	44409	Strait Jacket	Haloperidol + Promethazine + Chlorpromazine	Chlorpromazine			
27	44419	Lorazepam	Haloperidol + Promethazine				
28	44420	Diazepam					
29	44420	Zuclopenthixol					
30	44421	Olanzapine	Promethazine	Haloperidol + Promethazine + Chlorpromazine	Diazepam	Strait Jacket	
31	44433	Lorazepam	Promethazine	Haloperidol + Promethazine + Chlorpromazine			
32	44433	Haloperidol + Promethazine + Chlorpromazine	Diazepam				
33	44436	Haloperidol + Promethazine	Promethazine				
34	44438	Strait Jacket	Haloperidol + Promethazine + Chlorpromazine	Lorazepam			
35	44438	Diazepam + Lorazepam + Promethazine					
36	44440	Diazepam	Diazepam	Promethazine	Chlorpromazine	Zuclopenthixol	Promethazine
37	44441	Diazepam	Haloperidol + Promethazine				
38	44466	Strait jacket	Promethazine	Chlorpromazine	Promethazine	Haloperidol + Promethazine + Chlorpromazine	
39	44466	Chlorpromazine + Promethazine					

Appendix E: Source Full SoF Tables

Table E1: Straitjacket/Restraints (comparison 1, 2 and 3 of Table 4.2)

1: Restraints compared to seclusion for people with serious mental illnesses					
Patient or population: patients with people with serious mental illnesses Settings: Intervention: Restraints Comparison: seclusion					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Seclusion	**Restraints**			
Became tranquil or asleep/ episode over	**Moderate**		**RR 0.96** (0.7 to 1.3)	131 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	600 per 1000	**576 per 1000** (420 to 780)			
Global state: Needing medium/high doses of medication/extra medication	**Moderate**		**RR 1.15** (0.75 to 1.77)	131 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	300 per 1000	**345 per 1000** (225 to 531)			
Mental state: Average score (PANSS aggression)		The mean mental state: average score (PANSS aggression) in the intervention groups was **1.4 lower** (4.91 lower to 2.11 higher)		26 (1 study)	⊕⊕⊖⊖ **low**[2,3]
Mental state	No study reported binary outcomes for mental state.				
Adverse events: serious	**Moderate**		**RR 0.18** (0.04 to 0.94)	131 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	100 per 1000	**18 per 1000** (4 to 94)			
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;**					

Footnotes

[1] Indirectness: rated 'serious' as outcomes are pooled that are not quite the same as each other although both focus on end of episode.
[2] Indirectness: rated 'serious' as measure is a scale rather than the binary measure prespecified in protocol.
[3] Imprecision: rated 'serious' as study was small and confidence intervals are wide.

Table E2: Restraint by Bracer

2: Restraint by 'bracer' (protective restraint) compared to restraint by straitjacket (traditional constraint) for people with serious mental illnesses					
Patient or population: patients with people with serious mental illnesses Settings: Intervention: Restraint by 'bracer' (protective restraint) Comparison: restraint by straitjacket (traditional constraint)					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Restraint by straitjacket (traditional constraint)	**Restraint by 'bracer' (protective restraint)**			
Global state: Not improved - impulsiveness	**Moderate**		**RR 0.67** (0.2 to 2.2)	88 (1 study)	⊕⊖⊖⊖ **very low**[1,2]
	150 per 1000	**101 per 1000** (30 to 330)			
Global state: Not improved - injury	**Moderate**		**RR 0.71** (0.25 to 2.08)	88 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]
	200 per 1000	**142 per 1000** (50 to 416)			
Satisfaction: not satisfied - patients	**Moderate**		**RR 0.97** (0.83 to 1.14)	88 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	900 per 1000	**873 per 1000** (747 to 1000)			
Satisfaction: not satisfied - family	**Moderate**		**RR 0.39** (0.2 to 0.75)	88 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	500 per 1000	**195 per 1000** (100 to 375)			
Adverse events - abrasion	**Moderate**		**RR 3.67** (1.1 to 12.25)	88 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	100 per 1000	**367 per 1000** (110 to 1000)			
Adverse events - bruising	**Moderate**		**RR 5** (1.16 to 21.52)	88 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	50 per 1000	**250 per 1000** (58 to 1000)			
Adverse events - circulatory constraint (limbs)	**Moderate**		**RR 9** (1.19 to 68.07)	88 (1 study)	⊕⊕⊖⊖ **low**[2,3]
	50 per 1000	**450 per 1000** (60 to 1000)			
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;**					

Footnotes

[1] Indirectness: rated 'serious' as this outcome is specific rather than the pre-stated general overall impression of improvements or lack of them pre-specified in the protocol.
[2] Imprecision: rated 'serious' as study was small and confidence intervals are wide.
[3] Risk of bias: rated 'serious' as randomisation not well described, blinding impossible.

Table E3: Restraint compared to language-body comfort

3: Restraints compared to language-body comfort approach for people with serious mental illnesses					
Patient or population: patients with people with serious mental illnesses Settings: Intervention: Restraints Comparison: language-body comfort approach					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE) Comments**
	Assumed risk Language-body comfort approach	**Corresponding risk Restraints**			
Became tranquil or asleep/ episode over: (not 'angry')	**Moderate 900 per 1000**	**549 per 1000** (441 to 675)	**RR 0.61** (0.49 to 0.75)	120 (1 study)	⊕⊕⊖⊖ **low**[1,2]
Mental state: Average score (BPRS)		The mean mental state: average score (bprs) in the intervention groups was **4.8 higher** (0.62 lower to 10.22 higher)		120 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4]
Mental state - anxiety	**Moderate 100 per 1000**	**329 per 1000** (153 to 707)	**RR 3.29** (1.53 to 7.07)	120 (1 study)	⊕⊕⊖⊖ **low**[1,5]
Mental state - depression	**Moderate 100 per 1000**	**400 per 1000** (161 to 996)	**RR 4** (1.61 to 9.96)	120 (1 study)	⊕⊕⊖⊖ **low**[1,5]
Mental state - fear	**Moderate 100 per 1000**	**475 per 1000** (172 to 1000)	**RR 4.75** (1.72 to 13.13)	120 (1 study)	⊕⊕⊖⊖ **low**[1,5]
Mental state - nervous	**Moderate 100 per 1000**	**338 per 1000** (167 to 682)	**RR 3.38** (1.67 to 6.82)	120 (1 study)	⊕⊕⊖⊖ **low**[1,5]
Adverse events: any	**Moderate 0 per 1000**	**-2147483648 per 1000** (-2147483648 to -2147483648)	See comment	120 (1 study)	⊕⊖⊖⊖ **very low**[1,6] Risks calculated from pooled risk differences
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;**					

Footnotes

[1] Risk of bias: rated 'serious' - randomisation unclear, blinding impossible.
[2] Indirectness: rated 'serious' - 'not angry' proxy for end of aggressive episode.
[3] Indirectness: rated 'serious' - continuous measure, not binary.
[4] Imprecision: rated 'serious' - wide confidence intervals.
[5] Indirectness: rated 'serious' - list of very specific mental state effects rather than the broad outcomes required by the protocol.
[6] Imprecision: rated 'very serious' - no adverse effects or events reported but seems unlikely, possible under-reporting.

Table E4: Chlorpromazine compared to haloperidol for psychosis induced aggression or agitation

Patient or population: patients with psychosis induced aggression or agitation Settings: in hospitals of over 30 years ago Intervention: CHLORPROMAZINE Comparison: HALOPERIDOL					**September 2017 update** 1 study added to SoF table from 2010 review	
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	HALOPERIDOL	**CHLORPROMAZINE**				
Global outcome: Number of additional injections - 2-4 injections**	**667 per 1000**	**600 per 1000** (347 to 1000)	**RR 0.9** (0.52 to 1.55)	161 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	
Global outcome: Number of additional injections - 5 or more**	**267 per 1000**	**200 per 1000** (53 to 745)	**RR 0.75** (0.2 to 2.79)	161 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	
Adverse effects - cardiovascular - hypotension**	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 5** (0.26 to 96.13)	161 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	Serious adverse event
Adverse effects - movement disorders - extrapyramidal side effects	See comment	See comment	Not estimable	161 (2 studies)	See comment	No events[3]
Adverse effects - seizures**	**0 per 1000** (0 to 0)		**RR 3** (0.13 to 68.26)	161 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	
Leaving the study early**	**67 per 1000**	**134 per 1000** (13 to 1000)	**RR 2** (0.2 to 19.78)	30 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	(Ahmed, Jones, & Adams, 2010)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
**Medium risk/Study population
CI: Confidence interval; RR: Risk ratio;

Footnotes
[1] Randomisation not well described, blindness unlikely, selective reporting
[2] Small study
[3] Unusual not to experience any such effects, even in short term

Table E5: Promethazine compared to anything for psychosis induced aggression or agitation (Comparison 11 of table 4.2)

					September 2017 update 6 studies identified but none relevant	
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	PROMETHAZINE	**ANYTHING**				
Any outcome relevant to acute aggression or agitation	No relevant trial exists.					

Table E6: Haloperidol + promethazine compared to antipsychotic haloperidol for psychosis induced aggression (Comparison 12 of table 4.2)

Patient or population: people with psychosis-induced aggression **Settings:** **Intervention: HALOPERIDOL + PROMETHAZINE** **Comparison: ANTIPSYCHOTIC - HALOPERIDOL**					**September 2017 update** 1 study found Abolhassanzadeh 2015 (n=100) and added into review's SoF	
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	ANTIPSYCHOTIC - HALOPERIDOL	**HALOPERIDOL + PROMETHAZINE**				
Tranquil or asleep[1]: Not tranquil or asleep - by 30 minutes	**500 per 1000**	**325 per 1000** (245 to 435)	**RR 0.65** (0.49 to 0.87)	416 (2 studies)	⊕⊕⊕⊕ **high**	
Global state[1]: Needing restraints or seclusion by 12 hours	**200 per 1000**	**166 per 1000** (56 to 488)	**RR 0.83** (0.28 to 2.44)	60 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
Adverse effects[1]: Specific and serious adverse effects by 24 hours (not death) Central nervous system - seizure	**10 per 1000**	**9 per 1000** (1 to 150)	**RR 0.95** (0.06 to 15.01)	298 (1 study)	⊕⊕⊖⊖ **low**[4,5]	
Adverse effect: Specific and serious - Death	No study reported this outcome					
Service outcomes[1]: Not discharged - by 2 weeks	**500 per 1000**	**415 per 1000** (320 to 535)	**RR 0.83** (0.64 to 1.07)	310 (1 study)	⊕⊕⊕⊕ **high**	
Specific behaviours: Average aggression score - by 12 hours Overt Aggression Scale	The mean specific behaviours: average aggression score in the intervention groups was **1.8 lower** (1.93 to 1.67 lower)			60 (1 study)	⊕⊕⊖⊖ **low**[3,6]	(Huf, Alexander, Gandhi, & Allen, 2016)
Economics: Costs of care	No study reported this outcome					

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

Footnotes

[1]Moderate control risk approximates to that of the included trial(s).
[2]Indirectness: rated 'serious' - pre-stated outcome was 'another episode of aggression' - proxy outcome used.
[3]Imprecision: rated 'serious' - sample size is small and confidence intervals wide.
[4]Indirectedness: rated 'serious' - pre-stated outcome was 'serious adverse event' - proxy outcome used.
[5]Imprecision: rated 'serious' - wide confidence intervals - rare events.
[6]Indirectedness: rated 'serious' - pre-stated outcome was 'specific behaviours' - proxy outcome used.

Table E7: Haloperidol + promethazine + chlorpromazine compared to anything for psychosis induced aggression or agitation (Comparison 12 in table 4.2)

					September 2017 update No studies identified	
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	HALOPERIDOL + PROMETHAZINE + CHLORPROMAZINE	**ANYTHING**				
Any outcome relevant to acute aggression or agitation	No relevant trial exists.					

Table E8: Zuclopenthixol acetate vs. standard drug care for acute schizophrenia and similar serious mental illnesses (Comparison 10 in table 4.2)

Patient or population: patients with acute schizophrenia and similar serious mental illnesses Settings: Intervention: ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comment:** No direct review relevant to Lebanon.
	Assumed risk	**Corresponding risk**				
	Control	**ZUCLOPENTHIXOL ACETATE versus STANDARD DRUG CARE**				
Sedation/tranquillisation: Not sedated - at four hours Follow-up: 9 days	**Moderate[1]**		**RR 0.74** (0.54 to 1)	40 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
	900 per 1000	**666 per 1000** (486 to 900)				
Global state: 1. Requiring supplementary medication - antipsychotics Follow-up: 3-9 days	**Moderate[1]**		**RR 1.49** (0.97 to 2.3)	134 (3 studies)	⊕⊕⊖⊖ **low**[2,3]	
	300 per 1000	**447 per 1000** (291 to 690)				
Global state: 2. Requiring 3 or more injections - over 7 days Follow-up: 7 days	**Low**		**RR 0.39** (0.18 to 0.84)	70 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
	200 per 1000					
	Moderate[1]					
	500 per 1000	**195 per 1000** (90 to 420)				
	High[1]					
	800 per 1000	**312 per 1000** (144 to 672)				
Mental state: 1. No important improvement Follow-up: 6-9 days	**Low[1]**		**RR 0.86** (0.39 to 1.86)	188 (2 studies)	⊕⊕⊖⊖ **low**[2,3]	
	100 per 1000	**86 per 1000** (39 to 186)				
	Moderate[1]					
	150 per 1000	**129 per 1000** (58 to 279)				
	High[1]					
	200 per 1000	**172 per 1000** (78 to 372)				
Adverse effects: Movement disorders - dystonia (spasmodic postural disorder) - by 24 hours	**Low[1]**		**RR 0.68** (0.34 to 1.36)	242 (3 studies)	⊕⊕⊖⊖ **low**[2,3]	(Jayakody, Gibson, Kumar, & Gunadasa, 2012)
	50 per 1000	**34 per 1000** (17 to 68)				
	Moderate[1]					
	100 per 1000	**68 per 1000** (34 to 136)				
	High[1]					
	150 per 1000	**102 per 1000** (51 to 204)				

***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Moderate risk similar to that in control group.
[2] Risk of bias: rated 'serious' - allocation unclear.
[3] Imprecision: rated 'serious' - small trial/s, wide confidence intervals.

Table E9: Benzodiazepines compared to placebo for psychosis induced aggression or agitation (Comparison 6 in table 4.2)

Patient or population: patients with psychosis-induced aggression or agitation
Settings: hospitals (Romania & US)
Intervention: BENZODIAZEPINES
Comparison: PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PLACEBO	BENZODIAZEPINES				
Tranquilisation or asleep- sedation - medium term Number of participants sedated Follow-up: 24 hours	**59 per 1000**[1]	**98 per 1000** (25 to 389)	**RR 1.67** (0.42 to 6.61)	102 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	
Global state - no improvement - medium term As defined in each study Follow-up: 24 hours	**569 per 1000**[1]	**353 per 1000** (227 to 552)	**RR 0.62** (0.4 to 0.97)	102 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	
Global state - need for additional medication - medium term Number of participants requiring additional medication Follow-up: 24 hours	**529 per 1000**[1]	**529 per 1000** (365 to 762)	**RR 1** (0.69 to 1.44)	102 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	
Adverse effects/events - extrapyramidal symptoms - medium term Number of instances of extrapyramidal symptoms Follow-up: 24 hours	**59 per 1000**[1]	**19 per 1000** (2 to 182)	**RR 0.33** (0.04 to 3.1)	102 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	
Satisfaction with treatment: from the perspective of consumer, family and informal care givers or professionals/carers at any point during the acute management stage	No study reported this outcome.					
Economic outcomes - cost-effectiveness - clinically important	No study reported this outcome.					(Zaman et al., 2017)

***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio;
GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[1] Assumed risk: mean baseline risk presented for single study. Equates with that of control group.
[2] Risk of bias: 'very serious' - 90% of trial authors and co-authors were employed by trial sponsors at the time of the study - downgraded by 1.
[3] Risk of bias: 'serious' - randomisation poorly described - downgraded by 1.
[4] Imprecision: 'serious' - small sample size - downgraded by 1

Table E10: Benzodiazepines compared to antipsychotics for psychosis induced aggression or agitation (Comparison 7 in table 4.2)

.

Patient or population: patients with psychosis-induced aggression or agitation Settings: hospitals (US, Canada, Israel, China, Australia) Intervention: BENZODIAZEPINES Comparison: ANTIPSYCHOTICS						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments** One trial found relevant to Lebanon (Srinath 2010) with sample size smaller than review n=60
	Assumed risk	**Corresponding risk**				
	ANTIPSYCHOTICS	**BENZODIAZEPINES**				
Tranquilisation or asleep- sedation - medium term vs haloperidol **Number of participants sedated** **Follow-up: mean 16 hours**	**Low**		**RR 1.13** (0.83 to 1.54)	434 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	
	100 per 1000	**113 per 1000** (83 to 154)				
	Moderate[5]					
	227 per 1000	**257 per 1000** (189 to 350)				
	High					
	500 per 1000	**565 per 1000** (415 to 770)				
Global state: no improvement - vs haloperidol - medium term **As defined in each study** **Follow-up: 24 hours**	**Low**		**RR 0.89** (0.71 to 1.11)	188 (5 studies)	⊕⊕⊖⊖ **low**[1,2]	
	77 per 1000	**68 per 1000** (55 to 85)				
	Moderate[3]					
	619 per 1000	**551 per 1000** (439 to 687)				
	High					
	933 per 1000	**830 per 1000** (662 to 1000)				
Global state: no improvement - vs olanzapine - medium term **As defined in each study** **Follow-up: 24 hours**	192 per 1000	353 per 1000 (203 to 610)	**RR 1.84** (1.06 to 3.18)	150 (1 study)	⊕⊖⊖⊖ **very low**[1,2,7]	
Global state - need for additional medication - medium term **Number of participants requiring additional medication** **Follow-up: 24 hours**	See comment	See comment	Not estimable	216 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,4]	High levels of heterogeneity between included studies (Chi^2 = 16.41; I^2 = 94%) - data not pooled.[4]

Adverse effects/events: 1. extrapyramidal symptoms - vs haloperidol - medium term **Number of instances of extrapyramidal symptoms** **Follow-up: 21 hours**	**Low**		**RR 0.13** (0.04 to 0.41)	233 (6 studies)	⨁⨁⨀⨀ **low**[1,2]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate[6]					
	186 per 1000	**24 per 1000** (7 to 76)				
	High					
	500 per 1000	**65 per 1000** (20 to 205)				
Satisfaction with treatment: from the perspective of consumer, family and informal care givers or professionals/carers at any point during the acute management stage	No study reported this outcome.					
Economic outcomes - cost-effectiveness	No study reported this outcome.					(Zaman et al., 2017)

***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[1] Risk of bias: 'serious' - most trials received funding from pharmaceutical institute and there was potential risk of selection bias.
[2] Imprecision: 'serious' - confidence intervals for best estimate of effect include both 'no effect' and appreciable benefit/harm.

[3] Assumed risk: calculated from the included studies - presents 3 risks based on the control group risks - 'moderate' risk equates with that of control group (61.9%).

[4] Inconsistency: 'serious' - one study indicated significant favour of antipsychotics, while the other study indicated favour for benzodiazepines (non-significant).

[5] Assumed risk: calculated from the included studies - presents 3 risks based on the control group risks - 'moderate' risk equates with that of control group (22.7%).

[6] Assumed risk: calculated from the included studies - presents 3 risks based on the control group risks - 'moderate' risk equates with that of control group (18.6%).

[7] Only one small study reporting data

Table E11: Benzodiazepines compared to antihistamines + antipsychotics for psychosis induced aggression or agitation (Comparison 8 in table 4.2)

Patient or population: patients with psychosis-induced aggression or agitation Settings: psychiatric hospitals (US, Canada, Israel, China, Australia) Intervention: BENZODIAZEPINES Comparison: ANTIHISTAMINES + ANTIPSYCHOTICS						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments** One trial found relevant to Lebanon (Srinath 2010) with sample size smaller than review n=60
	Assumed risk	**Corresponding risk**				
	ANTIHISTAMINES + ANTIPSYCHOTICS	**BENZODIAZEPINES**				
Tranquilisation or asleep- sedation - medium term - lorazepam vs. haloperidol+promethazine Number of participants sedated Follow-up: 2 weeks	**970 per 1000**[1]	**883 per 1000** (815 to 951)	**RR 0.91** (0.84 to 0.98)	200 (1 study)	⊕⊕⊖⊖ **Low**[2,3]	
Tranquilisation or asleep- sedation - medium term - midazolam vs. haloperidol+promethazine Number of participants sedated Follow-up: 2 weeks	**827 per 1000**[1]	**934 per 1000** (860 to 1000)	**RR 1.13** (1.04 to 1.23)	301 (1 study)	⊕⊕⊖⊖ **Low**[2,3]	
Global state - no improvement - medium term As defined in each study Follow-up: 2 weeks	**120 per 1000**[1]	**260 per 1000** (139 to 486)	**RR 2.17** (1.16 to 4.05)	200 (1 study)	⊕⊕⊖⊖ **Low**[2,3]	
Global state - need for additional medication - medium term Number of participants requiring additional medication Follow-up: 2 weeks	**30 per 1000**[1]	**40 per 1000** (9 to 174)	**RR 1.33** (0.31 to 5.81)	200 (1 study)	⊕⊕⊖⊖ **Low**[2,3]	
Adverse effects/events - extrapyramidal symptoms - medium term Number of instances of extrapyramidal symptoms	No study reported this outcome.					
Satisfaction with treatment: from the perspective of consumer, family and informal care givers or professionals/carers at any point during the acute management stage	No study reported this outcome.					

Economic outcomes - cost-effectiveness	No study reported this outcome.	(Zaman et al., 2017)

***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[1] Assumed risk: mean baseline risk presented for single study. Equates with that of control group.
[2] Risk of bias: 'serious' - non-blind, open label study.
[3] Imprecision: 'serious' - small sample size.

Table E12: Benzodiazepines + antipsychotics compared to antihistamines + antipsychotics for psychosis induced aggression or agitation (Comparison 9 in Table 4.2)

Patient or population: patients with psychosis-induced aggression or agitation Settings: psychiatric emergency room (Brazil) Intervention: BENZODIAZEPINES + ANTIPSYCHOTICS Comparison: ANTIHISTAMINES + ANTIPSYCHOTICS						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	ANTIHISTAMINES + ANTIPSYCHOTICS	**BENZODIAZEPINES + ANTIPSYCHOTICS**				
Tranquilisation or asleep-sedation - medium term Number of participants sedated Follow-up: 12 hours	**33 per 1000**[5]	**400 per 1000** (55 to 1000)	**RR 12** (1.66 to 86.59)	60 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	
Global state - no improvement - medium term As defined in each study Follow-up: 12 hours	**0 per 1000**[1]	**0 per 1000** (0 to 0)[2]	**RR 25** (1.55 to 403.99)	60 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	
Global state - need for additional medication - medium term Number of participants requiring additional medication Follow-up: 12 hours		The mean global impression - need for additional medication - medium term in the intervention groups was **0 higher** (0 to 0 higher)		60 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	Skewed data - see 'data and analysis'.
Adverse effects/events - extrapyramidal symptoms - medium term Number of instances of extrapyramidal symptoms Follow-up: 12 hours	**167 per 1000**[5]	**100 per 1000** (27 to 382)	**RR 0.6** (0.16 to 2.29)	60 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	
Satisfaction with treatment: from the perspective of consumer, family and informal care givers or professionals/carers at any point during the acute management stage	No study reported this outcome.					
Economic outcomes - cost-effectiveness	No study reported this outcome.					(Zaman et al., 2017)

***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Footnotes

[1] Assumed risk: mean baseline risk - only one trial reported with 0 events in the control group and 12 events in the intervention group.
[2] Corresponding risk: one trial reported 12 events in the intervention group (40%).
[3] Risk of bias: 'serious' - study funded by pharmaceutical institutes, potential risk of selection bias, performance bias and attrition bias.
[4] Imprecision: 'very serious' - only one study reported data for this outcome, data were skew.
[5] Assumed risk: mean baseline risk presented for single study. Equates with that of control group.

Appendix F: Information Leaflet

Dear Relative or Friend,

RE: TREC study (Rapid Tranquilisation Clinical Trial).

This hospital is taking part in the TREC study - helping to identify the very best treatment for agitated or aggressive people in an emergency situation. All drug treatments used in this hospital are safe, efficient, well established and familiar to the doctors and nurses. No one, anywhere in the world, knows which the very best drug is to use for the emergency situation in terms of speed of onset and recovery.

Once it is clear that your friend/relative is so disturbed/unwell that medication is needed, and the doctor looking after their care thinks them to be eligible for the TREC study, they are given one of two short acting sedating drug treatments (haloperidol + promethazine or haloperidol + promethazine + chlorpromazine). The choice of the treatment is made in fair, random, way, as in a lottery.

Participation in the study does not involve additional tests or examinations and everyone will receive the best care available. The TREC study has been approved by the Ethical Committee of Deir Salib Hospital.

If you want additional information, get in touch with TREC Collaborator in this hospital (Dr Souheil Hallit).

Thank you.

Joseph Dib

TREC Co-ordinator

Appendix G: Consent form

PATIENT CONSENT FORM

TREC-Lebanon

Division of Psychiatry & Applied Psychology
&
Psychiatric Hospital of the Cross

Dear friend,

You have been allocated to ***TREC-Lebanon*** – a trial studying two of the hospital's routine intervention drugs during emergency periods requiring rapid tranquilisation. While you were in a state of agitation, you were allocated to either a group receiving haloperidol + promethazine or haloperidol + promethazine +chlorpromazine. This trial is designed to see which, if any, of the groups work most efficiently.

As your participation was involuntary, you may still change your mind about being involved. You are free to withdraw at any point post reading this form but not after data has been collected and anonymised as the trial co-ordinator will not know who you are. Withdrawal does not require a reason.

What is the project about?

The project is looking at rapid tranquilisation between two of the hospital's routine interventions, and which works best.

Who is being asked to take part, and why?

Clinicians – that is doctors and nurses as they are part of the routine care treatment.
Patients – that is patients exhibiting an aggressive episode requiring rapid tranquilisation.

Has the research been of any personal benefit to me?

Yes, either interventions you may have received are aimed at calming you down during a state of aggression.

What will you do with the data?

Once data has been collected, they will be anonymized by the lead researcher and inputted onto a transcription form whereby they will be analyzed in order to see differences between both intervention groups.

If you have any questions or concerns, please don't hesitate to ask.

If you are interested in the results of the survey or if you wish to withdraw your data from ***TREC-Lebanon***, please contact the head researcher (contact details below)

THANK YOU FOR YOUR PARTICIPATION

Head Researcher: Joseph Dib
(joseph.dib@nottingham.ac.uk)
Hospital Research Director: Dr. Souheil Hallit
(souheilhallit@hotmail.com)

If you have any queries or complaints about this study, please contact the head researcher at the first instance.

If this does not resolve the query to your satisfaction, please write to the Administrator to the Division of Psychiatry & Applied Psychology's Research Ethics Sub-Committee (MS-DPAPEthics@nottingham.ac.uk, +44 (0)115 8232214) who will pass your query to the Chair of the Committee.

This study has been ethically approved by both the University of Nottingham and the Psychiatric Hospital of the Cross.

Appendix H: TREC Forms

Please answer the questions before you open the envelope, and leave the completed envelope in the TREC-Bin box

TREC Number: ☐

Bulletin/Medical Notes number: ☐

Patient's Name: ☐

How disturbed is this Person? ☐ Number (Choose only one option)

1- Moderately
2- Markedly
3- Extremely
4- One of the most disturbed people you have seen
5- Other, please describe ☐

In your opinion, which is the primary cause of this episode? ☐ Number (Choose only one option)

1. Psychosis
2. Intoxication
3. Dementia
4. Mental retardation
5. Other organic problem. Which one? ☐
6. Psychological distress
7. Unknown
8. Other. Which one? ☐

Further details: ☐

Time of completing this form: hh ☐ mm ☐

Signature: ☐

TREC number:

Medical no:

Follow up Form

Please take care completing this, Accuracy is important

Time of administration

Hour Minutes

	Calm or tranquil?	Asleep?	Straitjacket +/- Restraint?	Important adverse effects?	Left the ward?
20 minutes after TREC medication					
40 minutes after TREC medication					
60 minutes after TREC medication					
2 hours after TREC medication					

Have important adverse effects occurred? Yes No

If 'Yes', please describe which occurred, and when.

Other comments

Thank you.

TREC number

Dr. Stopwatch form

When the person arrives in the Emergency Room observe the situation.

When the person is given the TREC medication start the watch.

Time person was tranquilised

Tranquilisation = when you feel the person is peaceful (whether asleep or not).

Time person fell asleep

Any other comments

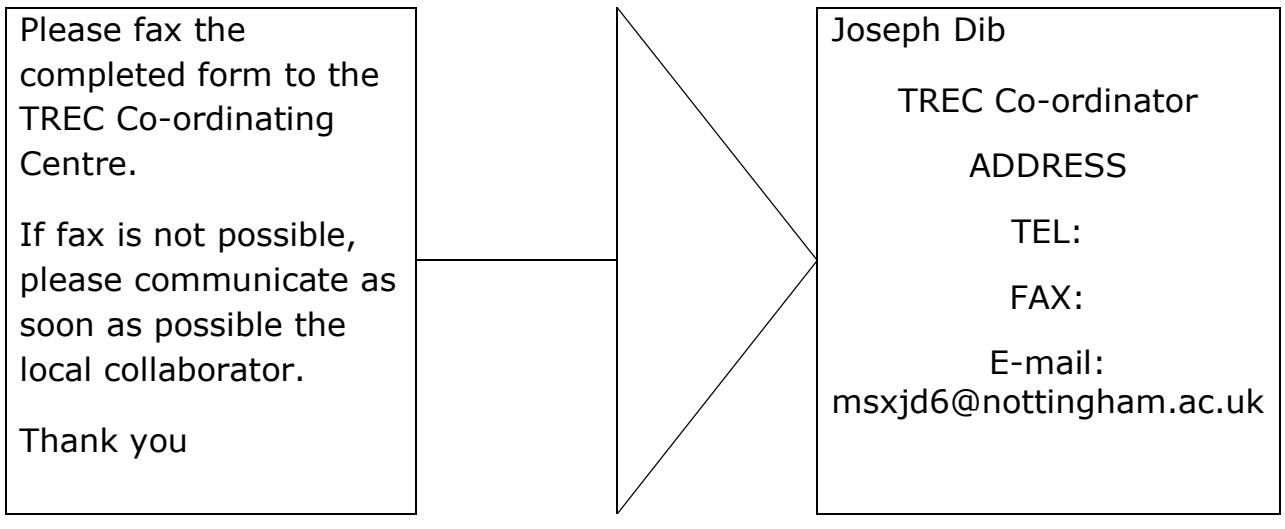
Serious Event Form

TREC NUMBER:

This form should be used to immediately notify the TREC Co-ordinator of any events that are serious and unexpected.

Details of unexpected serious event – when started, when ended, management, outcome

Patient's name	Name of responsible clinician
Hospital name	Bulletin or notes number
Signature of person completing form	Date form completed



Data transcription form

Initial data

Date of collection			
	day	month	year
Time of collection			
	hour	minutes	
TREC number			
ER / medical notes number			
Patient's name			
Sex			
	M / F		
Date of birth			
or	day	month	year
Approximate age		years	
Cause of agitation		Transcribe the number on the TREC envelope	
Diagnosis			
Severity of agitation		Transcribe the number on the TREC envelope	
Date TREC envelope was opened			
	day	month	year
Time TREC envelope was opened			
	hour	minutes	
Name of person who opened the TREC envelope			

TREC drug(s) [ ]

H+P / HPC

Drug(s) given during the first 24 hours

Name of drug	Dose	Route of administration*	Time	
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes
				hourminutes

* If oral, register only the time of first administration and the frequency that the drug was to be given, e.g. Twice/day or four times/ day

Were oral drugs refused in the first 24 hours?		Yes / No / Not applicable (not prescribed oral medication)

All these data should be on the prescription form. Is there anything you want to add? Please note it here.

Emergency Drug(s) given during the first 24 hours

Name of drug	Dose	Route of administration*	Time	
			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes
			hour	minutes

hourminutes

hourminutes

hourminutes

* If oral, register only the time of first administration and the frequency that the drug was to be given, e.g. Twice/day or four times/ day

Were oral drugs refused in the first 24 hours?		Yes / No / Not applicable (not prescribed oral medication)

All these data should be on the prescription form. Is there anything you want to add? Please note it here.

TREC Number

First psychiatric attendance?

Yes / No / Unknown

Already on antipsychotics?

Yes / No / Unknown

Where did the patient go immediately after administration of TREC drugs?

1-Transferred to ward

2- Left the ward

3- Transferred to another hospital

4- Other

In case of 'Ward of another hospital', which hospital?

In case of 'AWOL', at what time did the patient go AWOL?

Hour Minutes

In first the 24 hours after the use of TREC drugs, was the doctor was called to see the patient?	Yes / No / Unknown
Have important adverse reactions been registered on the notes or chart within the first 24 hours?	☐ Yes / No / Unknown

If they have been registered…

Type of reaction	Approximate time
☐	☐ ☐ hour minutes
☐	☐ ☐ hour minutes
☐	☐ ☐ hour minutes

How were the adverse effects managed?

All this information should be in the notes or ER chart. If there is anything you would like to add, please write it here.

Which one?

Do the notes record a diagnosis for this episode? [ ]

Were there other episodes of aggressiveness in first the 24 hours? [ ] Yes / No

If so…. [ ][ ] day [ ][ ] month [ ][ ] hour minutes

Calm or Tranquil	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Asleep	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Straitjacket+/-	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Restraint	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Important adverse effects?	20 minutes/ 40 minutes/ 60 minutes/ 2 hours

Left the ward?	20 minutes/ 40 minutes/ 60 minutes/ 2 hours
Was the doctor called?	Yes/ No/ Unknown

Any other comments	

Please, staple this to the primary outcome form, and give it to Joseph Dib.

Thank you.

Appendix I: Dummy Tables

Table I1: Characteristics of patients at trial entry

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Mean age (SD)		
Sex Male Female		
First psychiatric attendance Yes No Unknown		
*Severity of disturbance - first impression moderately markedly severely among the most extremely disturbed		
*Presumed cause for agitation Psychosis (schizophrenia or mania) Substance abuse Mental organic (dementia or oligophrenia) Clinical organic (metabolic, hormones, etc) Psychological Unknown		

* before opening the TREC envelope

Table I2: Compliance with the allocated treatment, and additional medication

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Already on antipsychotics?		
Yes No		
Allocated treatment		
No allocated treatment		
Non-Emergency Drugs in the first 24 hours (doses?)		
None		
Drug		
Drug		
Drug Drug Drug		
Emergency drugs in the first 24 hours (by class and route of administration)		
None		
Drug		
Drug Drug Drug		
Immediate placement		
Transferred to ward		
Left the ward		
Transferred to another hospital Other		

Table I3: Primary measures of outcome

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Tranquillisation		
% Tranquilised (Calm/Tranquil)		
By 20 minutes		
By 40 minutes		
By 60 minutes		
By 2 hours		

Table I3: Primary measures of outcome

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Tranquilisation (Calm or Tranquil after second agitated episode)		
% tranquillised after 2 hours		
Sleep		
% asleep By 20 minutes By 40 minutes By 60 minutes By 2 hours		
Straitjacket +/- Restraint Indicate whether patient had straitjacket only or included restraint		
% needing physical restraints after TREC drugs		
Mean time in physical restraints (SD)		
Revved Up Episode (Same agitated episode at different time Interval)		
By 20 minutes By 40 minutes By 60 minutes By 2 hours		
Second Agitated Episode (Agitated episode post 2 hours)		
Drugs used - by class and route of administration		
Adverse reactions		
Acute dystonia Mental confusion Akathisia (motor restlessness) Problems with vital signs Other		
Immediate placement		
Transferred to ward		
Left the ward		
Transferred to another hospital Other		
Was the doctor called?		
Yes No Unknown		

Table I5: Clinical progress / service outcomes / 2 weeks

	Haloperidol + Promethazine (n = …)	HPC (n = …)
Diagnosis (If applicable)		
Diagnosis at 2 weeks or diagnosis at time of discharge, if that was before 2 weeks		
Length of stay – time to discharge		
% discharged		
by 1 week		
by 2 weeks		

Appendix J: Ethics Forms

Figure J1: Lebanese ethics form

Dr. Joseph Dib

Reference number: HPC 001/2018

Title of Research: Trec Lebanon: a randomized control trial on agitated patient in the psychiatric settings

Dear Colleague,

During the meeting of 26 /02/2018, the committee deliberated on the above mentioned project. The committee unanimously considers that this project raises no ethical objection; therefore gladly notify you of his agreement and authorize you to proceed according to the proposed form.

We reserve the right to withdraw the agreement from the study at any time if circumstances change and in case of non-compliance with the principles and procedures of Research at HPC.

This authorization covers the period from 01/01/2018 to 01/01/2019. Any activity that exceeds this period requires a new agreement.

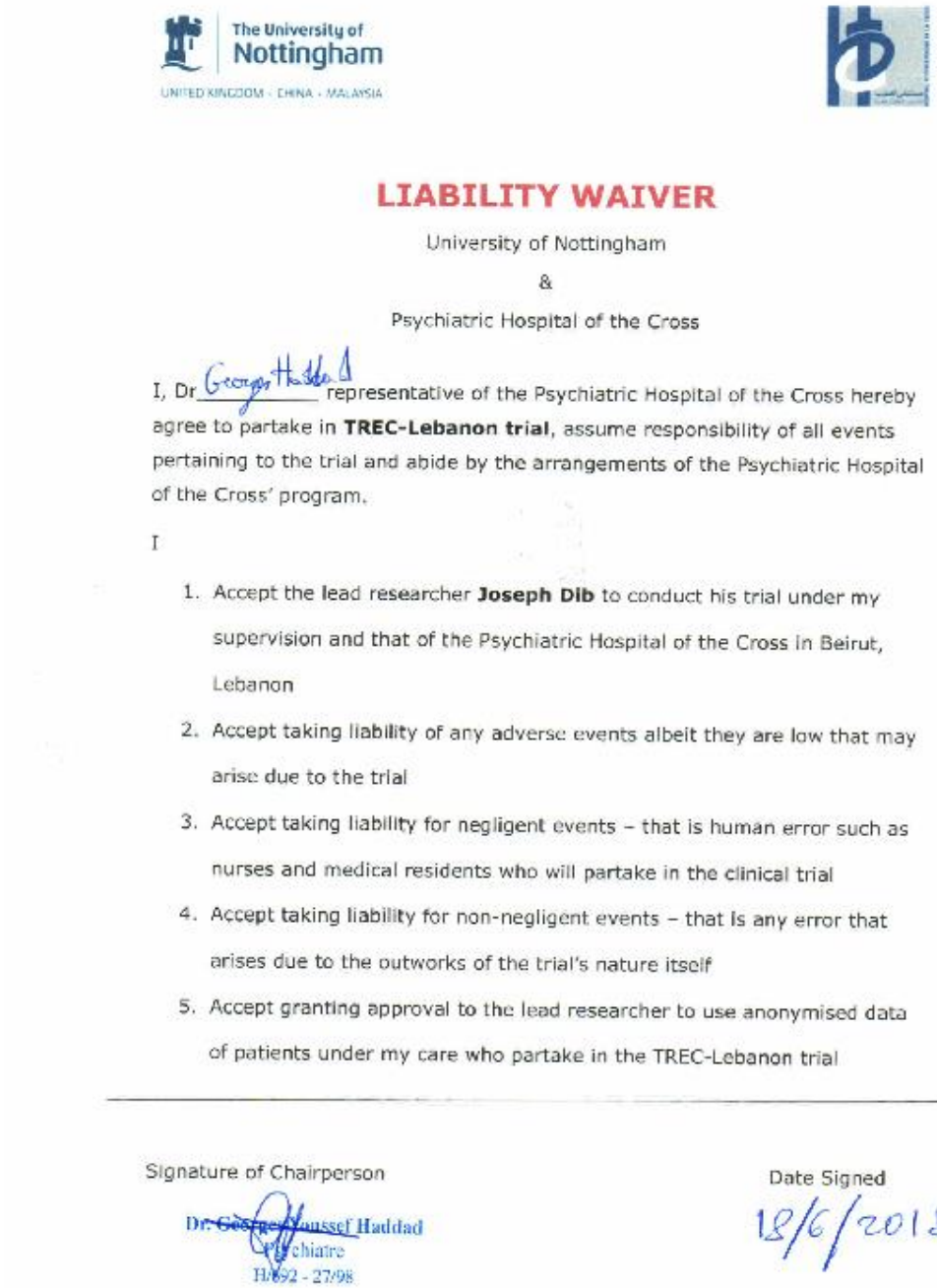
Please accept, dear colleague, the assurance of my highest consideration.

Georges Haddad
Chairman of the Committee

Date

26.02.2018

Figure J2: Liability waiver



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LIABILITY WAIVER

University of Nottingham

&

Psychiatric Hospital of the Cross

I, Dr George Haddad representative of the Psychiatric Hospital of the Cross hereby agree to partake in **TREC-Lebanon trial**, assume responsibility of all events pertaining to the trial and abide by the arrangements of the Psychiatric Hospital of the Cross' program.

I

1. Accept the lead researcher **Joseph Dib** to conduct his trial under my supervision and that of the Psychiatric Hospital of the Cross in Beirut, Lebanon
2. Accept taking liability of any adverse events albeit they are low that may arise due to the trial
3. Accept taking liability for negligent events – that is human error such as nurses and medical residents who will partake in the clinical trial
4. Accept taking liability for non-negligent events – that is any error that arises due to the outworks of the trial's nature itself
5. Accept granting approval to the lead researcher to use anonymised data of patients under my care who partake in the TREC-Lebanon trial

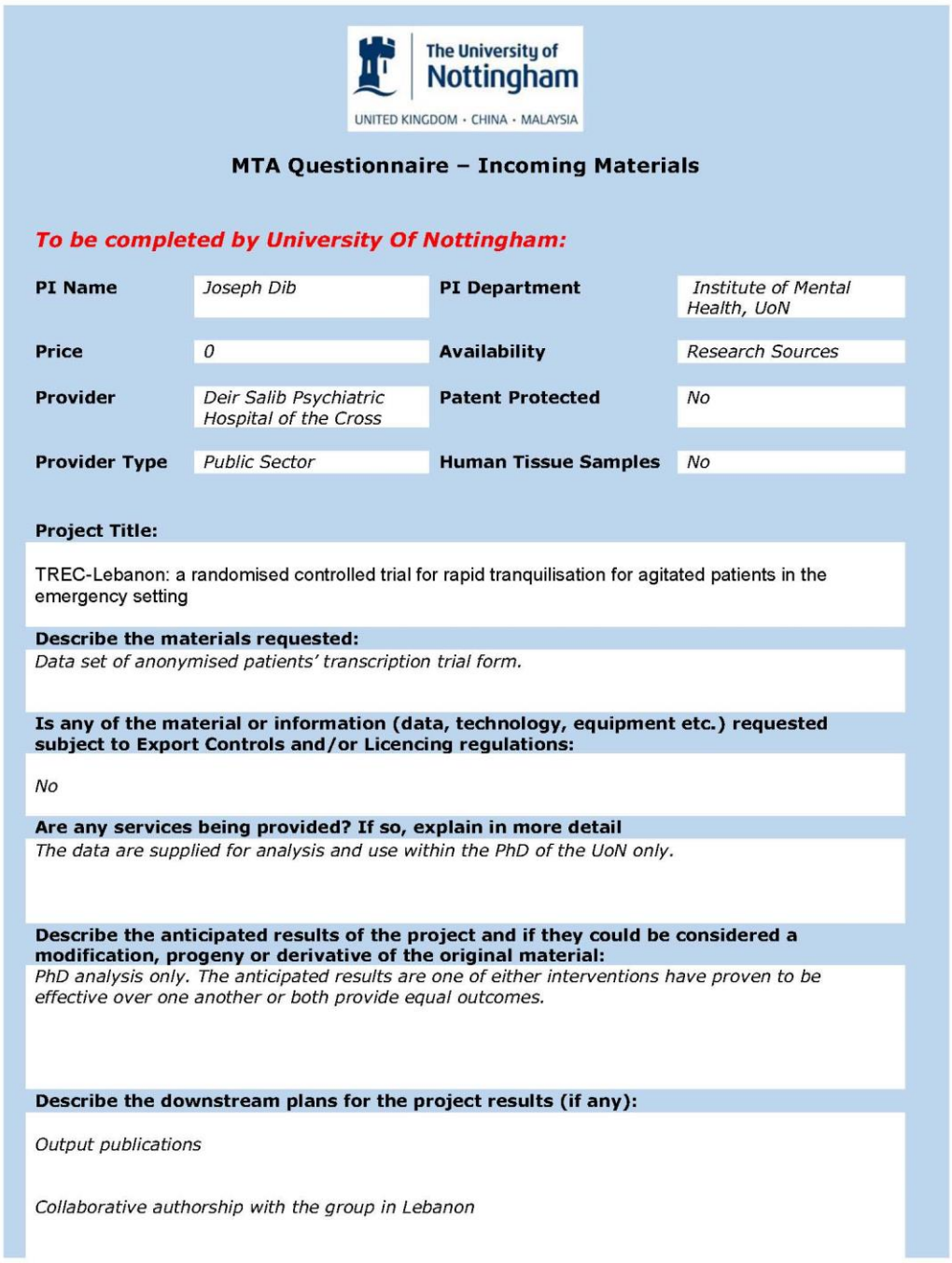
Signature of Chairperson

Dr. George Youssef Haddad
Psychiatre
H/692 - 27/98

Date Signed

18/6/2018

Figure J3: MTA questionnaire



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MTA Questionnaire – Incoming Materials

To be completed by University Of Nottingham:

PI Name	*Joseph Dib*	**PI Department**	*Institute of Mental Health, UoN*
Price	*0*	**Availability**	*Research Sources*
Provider	*Deir Salib Psychiatric Hospital of the Cross*	**Patent Protected**	*No*
Provider Type	*Public Sector*	**Human Tissue Samples**	*No*

Project Title:

TREC-Lebanon: a randomised controlled trial for rapid tranquilisation for agitated patients in the emergency setting

Describe the materials requested:

Data set of anonymised patients' transcription trial form.

Is any of the material or information (data, technology, equipment etc.) requested subject to Export Controls and/or Licencing regulations:

No

Are any services being provided? If so, explain in more detail

The data are supplied for analysis and use within the PhD of the UoN only.

Describe the anticipated results of the project and if they could be considered a modification, progeny or derivative of the original material:

PhD analysis only. The anticipated results are one of either interventions have proven to be effective over one another or both provide equal outcomes.

Describe the downstream plans for the project results (if any):

Output publications

Collaborative authorship with the group in Lebanon

Any factors that we should be aware of (e.g. time pressures, funder obligations, third party requiring access to materials):

All needs to be done within an adequate time frame in respect with the PhD timetable.

Please return completed to *BB-Contract-Request@exmail.nottingham.ac.uk*

Information to be requested from Provider

Contact Details of the PI/Lead Scientist and Contracts Officer (or equivalent):

PI/Lead Scientist's full-name:	Dr. Georges Haddad
Address:	Deir Salib Psychiatric Hospital of the Cross, Jal l Dib, Beirut, Lebanon.
E-mail and phone number	+961 4 710 225
Contracts Officer (or equivalent):	Dr. Souheil Hallit
Address:	Deir Salib Psychiatric Hospital of the Cross, Jal l Dib, Beirut, Lebanon.
E-mail and phone number:	souheilhallit@hotmail.com

Please return completed to:
BB-Contract-Request@exmail.nottingham.ac.uk

=

Appendix K: Full Dataset of Drugs Prescribed

Table K1: Non-routine emergency drugs per patient

Non routine drugs						
TREC-Drug Group	Treatment 1	Treatment 2	Treatment 3	Antipsychotic	Benzodiazepine	Anticholinergic
HP	Lorazepam				1	
HP	Lorazepam	Diazepam			2	
HPC	Lorazepam				1	
HPC	Diazepam				1	
HP	Chlorpromazine			1		
HPC	HP	Trihexyphenidyl		1		1
HPC	Lorazepam	Scheduled for ECT			1	
HPC	Lorazepam				1	
HP	Lorazepam	Haloperidol	Zuclopenthixol		1	
HP	Lorazepam				1	
HPC	HP			1		
HP	Quetiapine			1		
HP	Diazepam				1	
HP	Lorazepam				1	
HPC	Diazepam	HP			1	
HP	Diazepam				1	
HP	Diazepam	Promethazine	Chlorpromazine	1	1	1
HP	Lorazepam	Quetiapine		1	1	
HPC	Diazepam				1	
HP	Straitjacket					
HPC	HPC			1		
HPC	HP			1		
HP	Zuclopenthixol			1		
HPC	HPC			1		
HP	HPC	Straitjacket		1		
HPC	Promethazine	Diazepam			1	1
HP	Diazepam				1	
HP	Clonazepam				1	
HPC	HPC			1		
HP	HPC			1		
HPC	Promethazine	Diazepam			1	1
HPC	Straitjacket					
HP	Quetiapine			1		
HPC	Straitjacket					
HP	Straitjacket					
HP	Zuclopenthixol			1		
GROUP HP	20			9	12	1

GROUP HPC	16	6	9	2
36 patients total		15	21	3
RR[CI] HP: 48 HPC: 52		1.63 [0.62, 4.23]	1.44 [0.67, 3.12]	0.54 [0.05, 5.78]
ITT 1 HP: 43 HPC: 51		1.78 [0.69, 4.60]	1.58 [0.74, 3.39]	0.59 [0.06, 6.32]
ITT 2 HP:48 HPC: 51		1.59 [0.61, 4.14]	1.42 [0.66, 3.06]	0.53 [0.05, 5.67]
ITT 3 HP: 43 HPC: 52		1.81 [0.70, 4.69]	1.61 [0.75, 3.46]	0.60 [0.06, 6.44]

Table K2: Routine drugs per patient

Non routine drugs												
TREC-Drug group	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6	Anti-psychotic	Benzo-diazepine	Anti-cholinergic	Mood Stabiliser	Anti-depressants	Other
HP	Lithium Carbonate	Risperidone					1			1		
HPC	Valproic Acid	Paracetamol	Quetiapine				1			1		1
HPC	Valproic Acid	Quetiapine	Risperidone	Lithium	Metformin	Vildagliptin	2			2		2
HP	Aripiprazole	Lithium	Venlafaxine	Gabapentin	Topiramate		1			1	1	2
HPC	Risperidone	Lithium					1			1		
HP	Chlorpromazine						1					
HPC	Risperidone						1					
HP												
HP												
HPC	Valproic Acid	Promethazine							1	1		
HP												
HPC	Lithium	Haloperidol	Chlorpromazine						2	1		
HPC	Diazepam	Chlorpromazine	Lithium Carbonate	Aripiprazole			2	1		1		
HP	Pregabalin	Sertraline	Olanzapine	Magnecalm			1				1	2
HPC	Risperidone	Valproic Acid	Promethazine				1		1	1		
HPC	Risperidone						1					
HP												
HP	Risperidone	Lithium	Lorazepam				1	1		1		
HP	Risperidone	Promethazine					1		1			
HP	Olanzapine	Lithium	Carbamazepine				1	1		1		
HPC	Promethazine	Sertraline							1		1	
HPC	Valproic Acid	Quetiapine	Lorazepam				1	1		1		
HPC	Olanzapine	Trihexyphenidyl	Promethazine	Lorazepam	Fenofibrate	Valproic Acid	1	2	1	1		1
HP	Paliperidone	Quetiapine					2					
HPC	Risperidone	Valproic Acid					1			1		
HP	Olanzapine						1					
HP	Haloperidol	Trihexyphenidyl	Valproic Acid	Clonazepam	Amoxicillin		1	2		1		1
HP	Clozapine	Valproic Acid	Chlorpromazine				2			1		
HPC	Risperidone	Chlorpromazine					2					
HP	Olanzapine	Valproic Acid	Promethazine	Lorazepam			1	1	1	1		
HPC	Risperidone	Promethazine	Lithium				1		1	1		
HPC	Valproic Acid	Olanzapine	Diazepam	Chlorpromazine	Promethazine		2	1	1	1		
HP	Risperidone	Chlorpromazine	Promethazine				2		1			

HP	Clozapine	Lorazepam	Promethazine				1	1	1			
HPC	Valproic Acid	Diazepam	Quetiapine	Promethazine	Ketoprofen		1	1	1	1		1
HPC	Risperidone	Valproic Acid	Promethazine	Lorazepam			1	1	1	1		
HPC	Olanzapine	Diazepam	Chlorpromazine	Promethazine			2	1	1			
HPC	Bromelain	Valproic Acid	Clonazepam	Promethazine				1	1	1		1
HP	Lithium	Risperidone	Lorazepam				1	1		1		
HPC	Haloperidol	Trihexyphenidyl	Promethazine	Chlorpromazine			2	1	1			
HP	Sertraline	Clonazepam	Olanzapine	Promethazine	Neurotop		1	1	1		1	1
HP												
HPC	Valproic Acid	Aripiprazole	Lorazepam	Chlorpromazine			2	1		1		
HPC	Haloperidol	Chlorpromazine	Promethazine	Lorazepam			2	1	1			
HP	Olanzapine	Diazepam	Promethazine				1	1	1			
HPC	Quetiapine	Lactulose					1					1
HPC	Gastrimut	Lithium Carbonat	Olanzapine	Diazepam	Promethazine		1	1	1	1		1
HP	Aripiprazole	Lorazepam	Quetiapine				2	1				
HPC	Lorazepam	Risperidone	Quetiapine				2	1				
HPC	Valproic Acid	Promethazine	Chlorpromazine	Lorazepam			1	1	1	1		
HP	Lithium	Aripiprazole	Promethazine	Nervine			1		1	1		1
HP	Olanzapine	Risperidone					2					
HP	Quetiapine	Chlorpromazine	Paracetamol				2					1
HP	Olanzapine	Promethazine	Chlorpromazine	Lorazepam			2	1	1			
HPC	Haloperidol	Promethazine	Esomeprazole	Chlorpromazine	Trihexyphenidyl	Lorazepam	2	2	1			1
HP	Diazepam	Risperidone					1	1				
HPC												
HPC	Clozapine	Chlorpromazine	Promethazine				2	1				
HPC	Valproic Acid	Risperidone	Promethazine	Clonazepam	Chlorpromazine	Clozapine	3	1	1	1		
HPC	Haloperidol	Diazepam	Valproic Acid				1	1		1		
HPC	Promethazine	Chlorpromazine					1		1			
HP	Clozapine	Valproic Acid	Lorazepam				1	1		1		
HP	Clozapine	Chlorpromazine	Trihexyphenidyl				2	1				
HP	Lithium	Olanzapine	Lorazepam				1	1		1		
HPC	Risperidone	Chlorpromazine	Promethazine	Diazepam	Paracetamol	Ketoprofen	2	1	1			2
HPC	Valproic Acid	Diazepam	Quetiapine	Chlorpromazine	Paracetamol	Ketoprofen	2	1		1		2
HP	Quetiapine	Diazepam	Promethazine	Ketoprofen			1	1	1			1
HP	Valproic Acid	Chlorpromazine	Promethazine	Lorazepam	Risperidone		2	1	1	1		
HP	Haloperidol	Trihexyphenidyl	Chlorpromazine	Clonazepam			2	2				
HPC	Quetiapine	Chlorpromazine	Promethazine	Valproic Acid			2		1	1		
HPC	Haloperidol	Diazepam	Chlorpromazine	Trihexyphenidyl	Carbamazepine	Lithium	2	2		1		1
HP	Chlorpromazine	Promethazine					1		1			
HP	Haloperidol	Chlorpromazine	Promethazine	Trihexyphenidyl	Lithium	Valproic Acid	2	1	1	2		

HPC	Haloperidol	Trihexyphenidyl	Valproic Acid	Chlorpromazine			2	1		1		
HPC												
HP	Clozapine	Lorazepam					1	1				
HP	Olanzapine	Fluoxetine					1				1	
HPC	Clozapine	Haloperidol	Trihexyphenidyl	Chlorpromazine	Promethazine		3	1	1			
HP	Haloperidol	Trihexyphenidyl	Lithium	Chlorpromazine			2	1		1		
HPC	Valproic Acid	Lithium	Quetiapine	Olanzapine	Quetiapine	Promethazine	3		1	2		
HP	Valproic Acid	Chlorpromazine	Lorazepam				1	1		1		
HPC	Lorazepam							1				
HPC	Paliperidone	Lorazepam	Promethazine				1	1	1			
HP	Clozapine	Valproic Acid	Lorazepam	Chlorpromazine	Stavine	Aspirin	2	1		1		2
HPC	Chlorpromazine	Quetiapine	Lithium	Promethazine			2		1	1		
HP	Diazepam	Quetiapine	Promethazine	Ketoprofen	Paracetamol		1	1	1			2
HP	Clozapine	Lorazepam	Manicarb	Fluoxentine			1	1			1	1
HPC	Risperidone	Chlorpromazine	Promethazine				2		1			
HPC	Olanzapine	Valproic Acid	Promethazine	Glucophage			1		1	1		1
HPC	Haloperidol	Promethazine	Chlorpromazine	Lorazepam			2	1	1			
HP												
HPC												
HP	Carbamazepine	Haloperidol	Trihexyphenidyl	Diazepam	Prostafine	Mictonorm	1	2				3
HPC	Haloperidol	Promethazine	Diazepam				1	1	1			
HPC	Haloperidol	Trihexyphenidyl					1	1				
HP	Lithium	Promethazine	Chlorpromazine	Lanolept			1		1	1		1
HPC	Chlorpromazine	Promethazine	Lorazepam	Lithium			1	1	1	1		
HP	Clozapine	Promethazine	Chlorpromazine	Lithium			2		1	1		
HPC	Valproic Acid	Chlorpromazine	Phenytoin	Cimetidine			1			1		2
TOTAL							124	60	45	50	6	35
HP TOTAL				**140**			55	28	15	19	5	18
HPC TOTAL				**160**			69	32	30	31	1	17
RR[CI] HP: 48 HPC: 52												
ITT 1 HP: 43 HPC: 51												
ITT 2 HP: 48 HPC: 51												
ITT 3 HP: 43 HPC: 52												

Appendix L: CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	249
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	249
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	191
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	191-192
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	207-209
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	211-214
	6b	Any changes to trial outcomes after the trial commenced, with reasons	313-320
Sample size	7a	How sample size was determined	199-200
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation			
Sequence	8a	Method used to generate the random allocation sequence	207
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	203

Allocation Concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	210
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	203
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	213
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	200
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	259
	13b	For each group, losses and exclusions after randomisation, together with reasons	259
Recruitment	14a	Dates defining the periods of recruitment and follow-up	316
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	261
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	261
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	267
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	267
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a

Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	275
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	305
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	320
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	288
Other information			
Registration	23	Registration number and name of trial registry	205
Protocol	24	Where the full trial protocol can be accessed, if available	www.clinicaltrials.gov
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	n/a