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WFSBP CONSENSUS PAPER

## Assessment and management of agitation in psychiatry: Expert consensus

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### ABSTRACT

**Background** Psychomotor agitation is associated with different psychiatric conditions and represents an important issue in psychiatry. Current recommendations on agitation in psychiatry are not univocal. Actually, an improper assessment and management may result in unnecessary coercive or sedative treatments. A thorough and balanced review plus an expert consensus can guide assessment and treatment decisions. **Methods** An expert task force iteratively developed consensus using the Delphi method. Initial survey items were based on systematic review of the literature. Subsequent surveys included new, re-worded or re-rated items. **Results** Out of 2175 papers assessing psychomotor agitation, 124 were included in the review. Each component was assigned a level of evidence. Integrating the evidence and the experience of the task force members, a consensus was reached on 22 statements on this topic. **Conclusions** Recommendations on the assessment of agitation emphasise the importance of identifying any possible medical cause. For its management, experts agreed in considering verbal de-escalation and environmental modification techniques as first choice, considering physical restraint as a last resort strategy. Regarding pharmacological treatment, the “ideal” medication should calm without over-sedate. Generally, oral or inhaled formulations should be preferred over i.m. routes in mildly agitated patients. Intravenous treatments should be avoided.

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### KEYWORDS

Agitation; assessment; psychiatric emergency; restraint; verbal de-escalation

## Introduction

Psychomotor agitation in patients with psychiatric conditions represents a frequent phenomenon and a clinically relevant issue in psychiatry, not only in emergency settings but also during hospitalisation or in outpatient psychiatric settings. Lindenmayer described the key features generally present in patients with agitation including restlessness with excessive or

semipurposeful motor activity, irritability, heightened responsiveness to internal and external stimuli, and an unstable clinical course (Lindenmayer 2000).

The United States Food and Drug Administration (FDA) noted that several fairly consistent definitions for this behavioural phenomenon are currently put forward in the scientific literature (Gill et al. 2005). The DSM-5 (APA 2013) defines agitation as an excessive motor

activity associated with a feeling of inner tension. The activity is usually non-productive and repetitious and consists of behaviours such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still. Even if aggression and violence are not core features of agitation, a progression of severity of agitation can lead to aggressive and violent behaviours (Nordstrom and Allen 2007; Zeller and Rhoades 2010). Despite these attempts in defining agitation, it remains a broad and multifactorial syndrome and there is still a lack of unequivocal agreement.

Agitation is associated with many psychiatric conditions, including schizophrenia, bipolar disorder, personality disorders (mainly antisocial and borderline personality disorders), general anxiety disorder, panic disorder, and major depression (Battaglia 2005; Fountulakis et al. 2008; Nordstrom and Allen 2007), as well as with substance use and/or intoxication (Citrome 2004; Battaglia 2005). Further, agitation may be the main clinical manifestation of several "organic" conditions such as central nervous system diseases, including Parkinson's disease, Alzheimer's disease, other types of dementia, encephalitis, and meningitis (Battaglia 2005; Lesser and Hughes 2006) and of a wide range of general medical conditions (e.g., thyrotoxicosis, hypoglycemias) and in those with brain traumas (Warren et al. 2003; Battaglia 2005).

As many as 1.7 million emergency department visits in the United States per year may involve agitated psychiatric patients (Allen and Currier 2004) and 20–50% of visits to psychiatric emergency services are by patients who are at risk of agitation (Allen and Currier 2004; Marco and Vaughan 2005). Little information on the epidemiology of agitation is available but reported prevalence rates range from 4.3 (Pascual et al. 2006) to 10% (Huf et al. 2005; Sachs 2006) in psychiatric emergency services. Thus, the economic burden of agitation episodes has not been sufficiently studied, given that agitation is a syndrome that may increase the use of hospital resources (Peiró et al. 2004; Warnke et al. 2011).

In relation to psychiatric conditions, agitation is a common syndrome specially in schizophrenia and bipolar disorder, calling for rapid attention. Patients with schizophrenia show agitated, aggressive or violent behaviour, mostly related to psychotic symptoms or other symptoms (e.g., threatening behaviour or anxiety) (Angermeyer 2000; Hasan et al. 2012). It has been found that 14% of hospitalised patients with schizophrenia showed agitation and violent behaviour on admission (Soyka 2002), that around 20% of them will have episodes of agitation during lifetime (Pilowski et al. 1992) and that schizophrenic patients are thought to

account for 900,000 annual visits to psychiatric emergency services in the USA (Piechniczek-Buczek 2006). When agitation is presented in bipolar disorder patients, it frequently represents the most prominent clinical manifestation during mania and particularly during mixed states (Perugi et al. 2001; Vieta and Valentí 2013; Pacchiarotti et al. 2013; Perugi et al. 2015), but also during any affective episode in the presence of mixed or depressive features (Shim et al. 2014; Vieta et al. 2014; Popovic et al. 2015). With respect to depression, agitation during a major depressive episode may indicate the presence of an underlying bipolar disorder (Angst et al. 2009) and may predict a high risk of mood switching (Iwanami et al. 2014). Noteworthy, the presence of agitation and racing/crowded thoughts during mixed depression were found to be associated with a higher risk of suicidal ideation (Balázs et al. 2006; Pacchiarotti et al. 2011; Popovic et al. 2015).

Given the clinical relevance and the global impact of agitation in psychiatry, a prompt evaluation of causative factors and immediate management are essential, since this may allow control to be gained over a potentially dangerous behaviour that could progress to violence. In addition, psychomotor agitation has been also described as a possible predictor of suicide behaviour (Sani et al. 2011; McClure et al. 2015). In fact, an ineffective management of agitation can result in an unnecessary use of coercive measures (involuntary medication, restraint, and seclusion), escalation to violence, adverse outcomes for staff and patients, and substantial economic costs to the healthcare system (Hankin et al. 2011). For these reasons, agitation remains an important therapeutic target, not only in the acute and/or emergency setting, but also with respect to the long-term care of the psychiatric patient (Battaglia 2005). In this context, it is crucial to refer to and follow empirically derived current best practises for assessing and managing agitation (Allen et al. 2005).

The currently available guidelines regarding the assessment and management of agitation discuss a wide range of pharmacological and non-pharmacological interventions for agitated patients. The American Association for Emergency Psychiatry (AAEP) (Holloman and Zeller 2012) with the *Project BETA (Best practises in Evaluation and Treatment of Agitation)*, The American College of Emergency Physicians' (ACEP) with the *Clinical Policy: Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department* (Lukens et al. 2006) and the Joint Commission on Accreditation of Healthcare Organisations and the Centres for Medicare and Medicaid with the proposed standards in Restraint and Seclusion (The Joint Commission 2000), are examples of

the different organisations that provide support and guidance for the treatment of the acute agitation in the Emergency Departments (ED). The United Kingdom National Institute for Health and Care Excellence (NICE) also issued a guideline (*Violence: The short-term management of disturbed/violent behaviour in in-patient settings and emergency departments -CG25-*) in 2005, which is currently in the process of updating. Recently, both the World Federation of Societies of Biological Psychiatry (WFSBP) and the Austrian Society for Neuro-Psychopharmacology and Biological Psychiatry have also developed general recommendations for the acute management of agitation in schizophrenia (WFSBP: *Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance*; Hasan et al. 2012) and about the treatment of agitation in psychiatric emergency services (*The treatment of agitation in psychiatric emergency*; Kasper et al. 2013).

The major aim of this report is to conduct a thorough and balanced review of research findings on the assessment and management of agitation in primary psychiatric conditions. Using the Delphi method we also aimed to integrate this scientific literature and the currently available guidelines into an expert consensus on assessment and clinical management of psychiatric agitation, based on clinical experience and judgment, as well as research evidence, in order to provide a synthesis of the current knowledge supporting clinical recommendations for this important topic.

## Methods

### Consensus methods

The present work has been driven by a panel of global international experts on severe mental health illnesses, selected according to an objective procedure based on a Scopus search of citations on the specific topic of acute psychiatric management and psychomotor agitation and related conditions (number of citations per candidate during the past 3 years). The most cited authors and some additional expert authors from key geographical areas were identified and invited by e-mail to participate; 91% agreed to participate. Participants were recruited from several countries: Argentina, Australia, Austria, Brazil, Canada, France, Germany, Greece, Hong Kong, Italy, Spain, UK and USA. Consensus procedures were agreed upon between all experts through e-mail correspondence and teleconference meetings.

These procedures were focussed on the discussion and integration of findings from peer reviewed published research on the topic, including reviews and

meta-analysis, as well as clinical trial reports and the most relevant guidelines on agitation, with the aim to integrate them into an expert consensus. An expert co-author (MG) was appointed to develop a first draught of a systematic review, to be circulated after initial review by the senior authors (EV, MB and IP).

The final section of this report, which summarises consensus statements, has been achieved through personal and group e-mail correspondence, and serial iterative versions of the report, in order to provide a final guide on the assessment and management of agitation in psychiatry.

### Search strategy and selection criteria

We performed an extensive literature search through different medical specialties that deal with this topic. We searched on the electronic database utilising MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, Scopus, ISI Web of Science, and the International Pharmaceutical Abstracts, using the following search terms, limited to human studies: *agitat\** AND *epidemiology*; *agitat\** AND (*clinical features* OR *symptom\**); *agitat\** AND *assessment* AND (*scale* OR *instrument*); *agitat\** AND *evaluation* AND (*scale* OR *instrument*); *agitat\** AND *diagnos\**; *agitat\** AND (*treatment* OR *management*); *agitat\** AND *antipsychotic*; *agitat\** AND *benzodiazepine*; *agitat\** AND *rapid tranquilisation*; *agitat\** AND *prevent\**.

Inclusion criteria for the literature research included: papers published (or in press) on adults (>18 years old), from December 1970 to January 2015 dealing with the topic of agitation in psychiatric illness. We only included papers addressing agitation in primary psychiatric conditions, considering agitation in dementia and delirium topics to be reviewed separately due to the important "organic" nature and the wide range of different approaches considered until the date. Regarding the pharmacological management of agitation, studies included for the final review were limited to randomised controlled trials, clinical trials, prospective and retrospective large cohort studies, and meta-analysis in human subjects. Editorials, narrative reviews, small naturalistic studies, case reports, animal or *in vitro* studies, and letters to the editor were excluded. Regarding the assessment of agitation other special reports, text books and chapters, agency reports, guidelines and governmental reviews were also considered to be included, due to the lack of randomised clinical trials or high quality large naturalistic studies or even systematic reviews and meta-analysis. The task force reviewed these materials for appropriateness to the topic and the quality of the work.

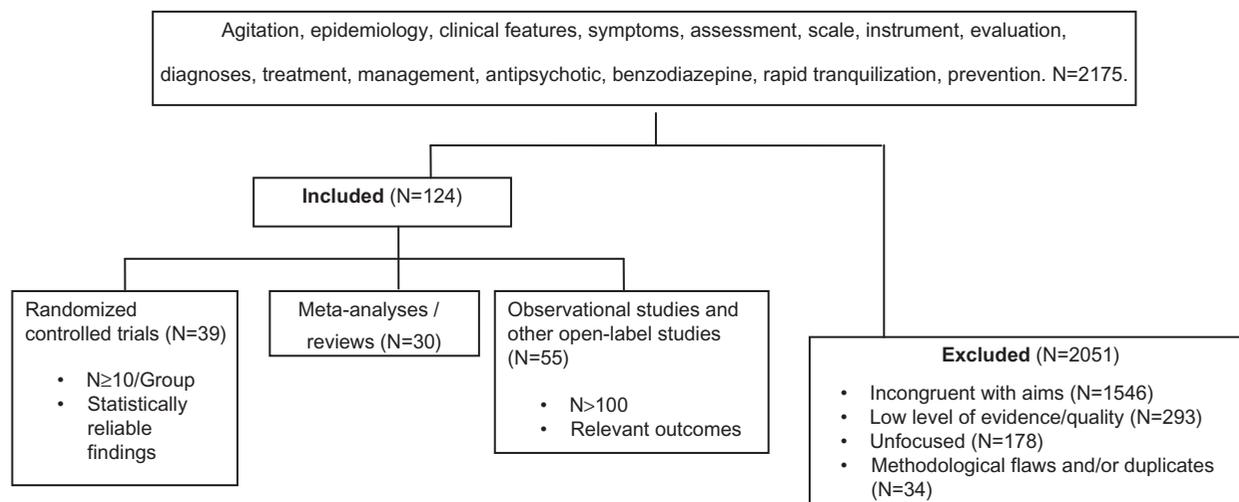


Figure 1. Flow diagram of study design and results in a review of psychomotor agitation in the psychiatric setting.

### Systematic review methods

Each report considered was rated for methodological quality according to the Jadad scale (Jadad et al. 1996) as poor (scores of 0–2) or acceptable-good (scores of 3–5). Each report was rated A, B, C or D for overall quality, as recommended by the Australian National Health and Medical Research Council (2009), save for the applicability criterion. Included references may contain additional reports for particular questions and statements. Meta-analysis and reviews were used as evidence to support information that could not be drawn from individual studies. Figure 1 outlines how reports were selected. The systematic review adhered to the PRISMA statement (Moher et al. 2015).

### Delphi method

To perform a table of agreed recommendations at the end of the systematic review, we conducted a survey using the Delphi method (Jones and Hunter 1995). Three survey rounds were conducted to develop consensus. The first survey included open-ended questions at the end of each section inviting participants to add comments and suggestions by e-mail. Later rounds were conducted online using eSurveysPro.com. The survey was sent to the members of the agitation task force for anonymous responses. Panel members rated survey items ranging from “essential” to “should not be included.” We calculated proportions of respondents rating each item. Survey items were classified as endorsed, re-rated, or rejected. The method used to conduct this survey is the same used to develop clinical recommendations by the ISBD Task Force on antidepressant use in bipolar disorders (Pacchiarotti et al. 2013).

### Endorsed items

Items rated by at least 80% of the international experts as essential or important were included in the recommendations.

### Re-rated items

Items rated as essential or important by 65–79% of panel experts were included in the next survey for re-rating after considering feedback from first-round results. Panel members could decide whether they wanted to maintain or change their previous rating on these relatively controversial items. Items were re-rated only once; if they did not achieve the criterion for endorsement, they were rejected.

### Rejected items

Items that were not included by at least 65% of panellists on the first round were rejected and excluded.

The initial survey included 52 items. The second survey included 33 items. The briefer third survey consisted of six items that needed re-rating. Twenty-two of the initial 33 items were endorsed and formed the section of the psychomotor agitation clinical recommendations of management and treatment (Table 1).

## Results

### Search results

A summary of our literature search and review is presented in Figure 1.

Table 1. Expert consensus recommendations on the assessment and management of psychomotor agitation.

Domain	Recommendation
Assessment: aetiology and differential diagnosis	1. Agitation with no provisional diagnosis or with no available information should be presumed to be from a general medical condition until proven otherwise.
Assessment: assessment tools	2. The routine medical examination in an agitated patient should include a complete set of vital signs, blood glucose measurement (finger stick), determination of oxygenation level, and a urine toxicology test.
Management: non-pharmacological intervention	3. After treating agitation, systematic assessment of sedation levels should be performed.
	4. The initial approach to a patient with agitation should always start with verbal de-escalation, environmental modifications and other strategies that focus on the engagement of the patient and not on physical restraint.
	5. Verbal de-escalation should be always used in cases of mild-to-moderate agitation, thus avoiding the need for physical restraint.
	6. Physical restraint should only be used as a last resort strategy when it is the only means available to prevent imminent harm.
	7. In front of risk of violence, the safety of patient, staff and others patients should be presumed.
	8. If restraint and seclusion are necessary, not only proper monitoring but the use of quality indicators should be also undertaken.
	9. In the case of physical restraint, vigilant documented monitoring should be mandatory. Vital signs should be measured every 15 min for 60 min and then every 30 min for 4 h or until awake.
	10. Physical restraint should be removed as soon as the patient is assessed to not to be dangerous anymore for him/herself and/or others.
Management: pharmacological intervention	11. Non-invasive treatments should be preferred over invasive treatments whenever possible.
	12. Agitated patients should be as much as possible involved in both the selection of the type and the route of administration of any medication.
	13. The main goal of pharmacological treatment should be to rapidly calm the agitated patient without over-sedation.
	14. When planning involuntary pharmacological treatment team consent should be reached and the action carefully prepared.
	15. Oral medications, including solutions and dissolving tablets, should be preferred to intramuscular route in mildly agitated patients.
	16. A rapid onset of the effect and the reliability of delivery are the two most important factors to consider in choosing a route of administration for the treatment of severe agitation.
	17. In the case of agitation secondary to alcohol withdrawal treatment with benzodiazepines should be preferred over treatment with antipsychotics.
	18. In the case of agitation associated with alcohol intoxication, treatment with antipsychotics should be preferred over treatment with benzodiazepines.
	19. In mild-to-moderate agitation, and when rapid effects of medication are needed, inhaled formulations of antipsychotics may be considered.
	20. The concomitant use of intramuscular olanzapine and benzodiazepines should be avoided, due to the possible dangerous effects induced by the interaction of the two medications in combination (hypotension, bradycardia, and respiratory depression).
Special subpopulations	21. Intravenous treatment should be avoided except in cases where there is no alternative.
	22. Elderly agitated patients should be treated with lower doses: usually between a quarter and a half of the standard adult dose.

### Assessment

The assessment of an agitated patient is complicated by several difficulties. The uncooperativeness and/or the inability to give a relevant history often force clinicians to make decisions based on very limited information. Usually, a complete psychiatric assessment cannot be completed until the patient is calm enough to participate in a psychiatric interview (Stowell et al. 2012). Administration of psychiatric interviews and self-rating scales may exacerbate agitated behaviours with the potential risk of rapidly escalating from agitation to aggressiveness or violence, that are not part of agitation per se but which often represent an important complication of such condition (Huber et al. 2008). Additionally, although an early identification of warning signs that could predict agitation, aggressive behaviours or violence would be also helpful, the escalation from

anxiety to agitated and violent behaviours is unpredictable in most cases (Hankin et al. 2011).

Another noteworthy issue is that agitation may be one of the main indicators of imminent and impulsive suicidal behaviours (Ribeiro et al. 2011; Sani et al. 2011; Bryan et al. 2014; McClure et al. 2015); clinicians should include an assessment of suicide risk severity early in the evaluation of agitated patients.

Unfortunately, there is still a lack of controlled studies comparing different methodologies or tools, due to the reasons above-mentioned. Most of information regarding this section comes from expert recommendations and consensus based on clinical experience. They should include a comprehensive approach to the aetiology, differential diagnosis, the use of assessment tools and the evaluation of the possible warning signs that may predict upcoming agitated behaviours.

## Aetiology and differential diagnosis

In the assessment process, clinicians should perform an initial mental status examination as soon as possible, aimed at determining the most likely cause of agitation, so as to guide preliminary interventions to calm the patient. Once the patient has been calmed, a more extensive psychiatric assessment can be completed. In this line, a definitive diagnosis is not considered a primary goal in the initial assessment of the agitated patient. On the contrary, ascertaining a differential diagnosis, determining safety, and developing an appropriate management strategy should be the main goal of the assessment (Stowell et al. 2012).

Agitation can be caused by a variety of aetiologies, both medical and psychiatric (Yildiz et al. 2003; Nordstrom et al. 2012), which converts agitation in one of the most commonly encountered clinical problems in psychiatric facilities and emergency services (Yildiz et al. 2003). A key step in the initial evaluation is to identify the underlying cause of the agitation in order to establish the best management approach. In the expert consensus of Allen et al. (2001), three general possible aetiologies of agitation were described: a general medical condition, substance intoxication, and a primary psychiatric disorder. More recently, the *project BETA* workgroup (Nordstrom et al. 2012), added a fourth category of "undifferentiated agitation" (Table 2). In contrast, the recent guidelines published by Kasper et al. (2013) proposed a more extensive classification

Table 2. Medical and psychiatric conditions that may cause agitation.

### Agitation from general medical condition

- Head trauma
- Encephalitis, meningitis or other infection
- Encephalopathy (particularly from liver or renal failure)
- Exposure to environmental toxins
- Metabolic derangement (e.g., hyponatremia, hypocalcaemia, hypoglycaemia)
- Hypoxia
- Thyroid disease
- Seizure (postictal)
- Toxic levels of medication (e.g., psychiatric or anticonvulsant)

### Agitation from intoxication/withdrawal

- Alcohol
- Other drugs (cocaine, ecstasy, ketamine, bath salts, inhalants, methamphetamines)

### Agitation from psychiatric disorder

- Psychotic disorder
- Manic and mixed states
- Agitated depression
- Anxiety disorder
- Personality disorder
- Reactive or situational agitation (adaptive disorder)
- Autism spectrum disorder

Undifferentiated Agitation (presumed to be from a general medical condition until proven otherwise)

Adapted from Nordstrom et al. (2012).

including: catatonic syndrome, manic syndrome, agitation depressive syndrome, disturbance of consciousness/delirium, suicidality, delusions, hallucinations, anxiety/panic syndrome, alcohol and/or drug use, and dementia. Thus, before any therapeutic decision is taken, it is necessary to establish a presumed differential diagnosis to categorise the patient in one of the diagnostic groups mentioned previously.

To achieve an accurate differential diagnosis of the agitation, the first step is to obtain vital signs, as much of a medical and psychiatric history, and perform a visual examination of the patient assessing their appearance, behaviour, level of awareness, attentional deficits, and cognitive skills (Allen et al. 2005). Additional information from collateral sources and medical records are also important to determine previous diagnoses and medications (Stowell et al. 2012). The initial assessment should be directed at identifying the underlying aetiology, particularly excluding the possibility of serious, life-threatening, medical conditions (Nordstrom et al. 2012). As a general rule, especially in an individual with no previous history of psychiatric illness, the agitation should be suspected to be due to a general medical condition until proven otherwise. The project BETA workgroup (Stowell et al. 2012; Nordstrom et al. 2012) suggests that psychiatrists should initially consider delirium, cognitive impairment and intoxication or withdrawal before thinking on a psychiatric disorder as a cause of the agitation. Abnormal vital signs and/or abnormal physical examination results, overt signs of alcohol or drug intoxication or withdrawal, evidence of exposure to toxins or decreased consciousness are all indicative of a delirium or a medical aetiology. Neurological problems should also be considered including head injury, stroke, Parkinson, and multiple sclerosis (Allen et al. 2001; Nordstrom et al. 2012; Stowell et al. 2012).

In emergency settings, it is not uncommon for a patient to go through an initial screening and have a diagnosis of delirium overlooked. The patient may be mistakenly diagnosed as being psychotic, based on the fact that physical signs and symptoms of delirium may be subtle and easily go undetected (Stowell et al. 2012). In the presence of delirium, the patient has an altered level of awareness and problems in directing, focussing, sustaining, or shifting attention (Stowell et al. 2012). Next, the examiner should consider if there is any cognitive impairment underlying the current state of agitation. Brief cognitive screening, using tools such as the Mini Mental State Examination or the Brief Mental Status Examination (Folstein et al. 1975; Kaufman and Zun 1995), could be administered when the patient is calm and able to participate. If cognitive impairment is

found, a collateral history is needed in order to determine whether or not it is of recent onset. The next step should be to assess whether the patient is intoxicated or in withdrawal. A history of a recent drug use is important to detect such conditions and clinicians should be able to recognise clinical symptoms depending on the different substances of use (Stowell et al. 2012).

The next and final issue regarding the differential diagnosis is whether the patient is agitated owing to a primary psychiatric condition. In a patient with pre-existing psychiatric disease who presents with symptoms similar to previous psychiatric episodes and with normal vital signs, little to no testing may be needed to confirm this (Nordstrom et al. 2012). In these cases, there are not alterations in the level of consciousness, the patients are awake and oriented and they rarely fluctuate. However, the routine examination should include vital signs, blood glucose (finger stick) and oxygenation level, if not obtained previously. If possible, blood sample testing including haemograms, electrolyte profile and renal function should be considered, as well as urine toxicology and pregnancy tests if the patient is a woman of child-bearing age (Allen et al. 2001; Stowell et al. 2012).

Once an acute medical cause of agitation is excluded, an accurate psychiatric and mental status evaluation should be performed. Agitation may present with different clinical manifestation across many psychiatric illnesses and there is no established standard psychiatric assessment (Citrome 2002; Stowell et al. 2012). The project BETA workgroup (Stowell et al. 2012) suggested that psychiatric assessment should include not only the interview with the patient, but also collateral information (medical records, interview with families, friends, outpatient care providers, or any other individuals who might know about the patient's history). History of the present illness, past psychiatric history, past medical history, substance use history, social history, family history, and the mental status examination should also be covered. Affective state, thought process, suicidal and homicidal ideation, the presence of psychotic symptoms, judgment/insight, executive functions, and reasoning and reliability must ultimately also be assessed (Stowell et al. 2012). Additionally, clinicians may also find auditory hallucinations (rarely visual hallucinations), persecutory and/or paranoid delusions (schizophrenia and related disorders), grandiosity (mania), inappropriate mood (elation or irritability), hostility or aggressive behaviour, and loud, rapid or pressure of speech (Hasan et al. 2012). Although acute agitation is commonly associated with psychotic diseases, such as schizophrenia, schizoaffective disorder and bipolar disorder (Schleifer 2011), several other psychiatric disorders should also

be considered in the psychiatric differential diagnosis including agitated depression, anxiety disorder, personality disorders, adjustment disorders or autism spectrum disorder.

### *Assessment tools in psychiatric agitation*

The majority of available expert consensus and several reviews highlight the fact that a prompt assessment of the agitated patient is critical for successful management (Allen et al. 2005; Marder 2006; Stowell et al. 2012; Kasper et al. 2013). Furthermore, to the clinical assessment of patients described in the section above, several psychometric tools have been used in the measurement of the severity of agitation, the risk of escalation to aggressive behaviours and in the assessment of the treatment response (Zeller and Rhoades 2010). These are described in turn in this section.

The literature search retrieved 53 references concerning assessment tools in agitation, of which 33 have been eliminated based on their title alone. Twenty remaining psychometric tools used across different treatment settings were retrieved. Of these tools, three were checklists designed to screen warning signs of aggression/violence in patients with agitation and they will be described more in detail in the section regarding risk factors for psychiatric agitation below. Of the 17 remaining tools, six were developed to be performed in non-primary psychiatric patients (e.g., dementia or brain injury) and two have not been validated in agitated patients with psychiatric illness, and so will not be considered further. The nine remaining tools specifically used in the screening and severity of the psychiatric agitation are listed in Table 3.

**Self-rated scales.** The Brief Agitation Measure (BAM) is a three-item inventory designed to capture the subjective experience of agitation, measuring levels of agitation within the past week in a seven-point likert scale of severity. This scale has been validated by Ribeiro and colleagues (2011) in two studies with two different samples: study 1 was composed of a non-clinical sample of 212 subjects (undergraduate students) and study 2 by a sample of 107 adult psychiatric outpatients. The authors concluded that the BAM is an easy and reliable screening measure in clinical and non-clinical populations that can be administered routinely or when elevated risk of imminent agitation is suspected. The BAM also demonstrated utility in the evaluation of the suicide risk although its use is always recommended in association with other tools

Table 3. Assessment tools for psychomotor agitation.

Psychometric Tools assessing psychomotor agitation in psychiatric settings.	
•	Agitation Severity Scale (ASS) (Strout 2014)
•	Behavioural Activity Rating Scale (BARS) (Swift et al. 1998)
•	Brief Agitation Measure (BAM) (Ribeiro et al. 2011)
•	Clinical Global Impression Scale for Aggression (CGI-A) (Huber et al. 2008)
•	Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield et al. 1989)
•	Overt Aggression Scale (OAS) (Silver and Yudofsky 1991)
•	Overt Agitation Severity Scale (OASS) (Yudofsky et al. 1997)
•	Positive and Negative Syndrome Scale Excited Component (PANSS-EC) (Kay et al. 1987)
•	Staff Observation Aggression Scale (SOAS) (Palmstierna and Wistedt 1987)
Checklists assessing agitation and aggressive/violent behaviours.	
•	Broset Violence Checklist (BVC) (Linaker and Busch-Iversen 1995)
•	The Historical, Clinical, Risk Management-20 (HCR-20) (Webster et al. 1997)
•	The McNeil-Binder Violence Screening Checklist (VSC) (McNeil and Binder 1994)

specifically focussed on the assessment of suicide risk (Ribeiro et al. 2011).

**Observer-rated scales.** The Agitation Severity Scale (ASS) is a very recent observation-based rating scale designed to assess severity in acute psychiatric patients in emergency settings. This 21-item scale evaluates behaviours involved in agitation. The ASS has been validated against the Overt Agitation Severity Scale (OASS) in a prospective observational study of 270 acute agitated psychiatric patients (Strout 2014). In this study, the ASS was found to be simple, not requiring the patient's participation, and useful when a rapid evaluation is needed, such as in the emergency settings.

The Behavioural Activity Rating Scale (BARS) (Swift et al. 1998) is also based on clinical observation. This measures the severity of agitated behaviour using a single item that describes seven levels of severity (from a state of sedation to a state of agitation). The BARS was validated by Swift et al. (1998) in 502 acutely agitated patients with psychosis against the Clinical Global Impression of Severity (CGI-S) scale and a cluster of agitation-related items from the Positive and Negative Syndrome Scale (PANSS). The BARS was described as being easy and valid to assess this population in terms of treatment efficacy for agitation. The usefulness of this scale, even for clinicians not trained in psychiatry or emergency medicine, has also been supported by the recent consensus of the project BETA workgroup (Nordstrom et al. 2012).

The Clinical Global Impression Scale for Aggression (CGI-A) is a single-item rated in a five-point likert scale of severity based solely clinical observation. Huber and colleagues (2008) validated this scale in an observational study with 558 agitated psychiatric patients (59.1%

schizophrenia spectrum disorders, followed by substance use, mood, and personality disorders). The authors found a strong linear correlation between the Positive and Negative Syndrome Scale Excited Component (PANSS-EC) and the CGI-A. Additionally, authors suggested that the CGI-A could be generalisable to a broad range of psychiatric patients treated for agitation and aggression.

The Cohen-Mansfield Agitation Inventory (CMAI) is a caregiver-rated questionnaire that helps in the screening of 29 agitated behaviours on a seven-point likert scale of severity (Cohen-Mansfield et al. 1989). The CMAI was firstly developed for the assessment of elderly patients in long-term care facilities, although it has been also used for the initial assessment of agitation in psychiatric wards (Shah et al. 1998). However, as suggested in a recent review (Strout 2014), the limitations of this scale, in particular the long observational time frame of 2 weeks prior to its administration, make the CMAI inappropriate to be routinely used in psychiatric emergency settings.

The Overt Aggression Scale (OAS) (Yudofsky et al. 1986) is an easily applicable tool that classifies aggressive episodes into four severity types: verbal aggression, aggression against objects, self-aggression and physical aggression against others. This scale was firstly designed and validated in an observational study performed in both adults and paediatric psychiatric patients in clinical and research settings (Yudofsky et al. 1986). Later, this tool has been used in an observational study of 137 schizophrenic patients to determine its sensitivity (0.80) and specificity (0.97), showing an adequate positive and negative predictive power on this population (Fresán et al. 2004).

The Overt Agitation Severity Scale (OASS) collects 47 agitated behaviours classified into 12 behaviourally related units. This tool has been firstly developed to assess the frequency and severity of agitated behaviours in a sample of elderly psychiatric inpatients (Yudofsky et al. 1997) but its reliability and validity in adult psychiatric inpatients has been also tested (Kopecky et al. 1998). However, in a recent observational study, it was found that OASS is not appropriate in an emergency setting due to its limitations, particularly the 15-min observation period required (Strout 2014).

The Positive and Negative Syndrome Scale Excited Component (PANSS-EC) (Kay et al. 1987) has been commonly used to measure severity agitation in acute psychotic patients and has been extensively used in pharmacological clinical trials for agitation. It includes five individual PANSS items: hostility, uncooperativeness, impulsivity, tension, and excitability. The PANSS-EC has been validated in an observational, multisite,

prospective study performed in acutely agitated psychotic patients in the emergency department (77% schizophrenia, 12.2% bipolar disorder) against the CGI-S, and the Agitation and Calmness Evaluation Scale (ACES) (Montoya et al. 2011). Although it was initially used as a research tool, the PANSS-EC has been also used in clinical practise to aid in deciding whether to administer psychotropic medication to agitated patients with schizophrenia (Breier et al. 2002). PANSS-EC has also been referred as one of the simplest and most intuitive scales used to assess psychotic agitated patients (Lindenmayer et al. 2008) and it has also been considered the preferred measure in modern trials (Breier et al. 2002; Sachs et al. 2007; Currier et al. 2007; Marder et al. 2007).

The Staff Observation Aggression Scale (SOAS) (Palmstierna and Wistedt 1987) has been developed to assess inpatient aggressive behaviours in psychiatric wards. It could be used to rate both the nature and the severity of aggressive incidents using a 5-columns rating: provocation, means used by patient, aim of aggression, consequences for the victim, measures to stop aggression. The psychometric properties of this scale have been reviewed through several studies being described as a useful tool to measure rates of prevalence and frequency of aggression as well as the severity of aggression in psychiatric acute patients (Nijman et al. 2005).

### *Risk factors for aggressive behaviours in agitated patients*

Agitation is a dynamic situation that may rapidly escalate from anxiety to aggressive or violent behaviours (Citrome and Volavka 2014). The avoidance of aggressive or violent behaviour relies on an early identification of individuals at risk of escalating agitated behaviour. Despite the literature suggests that, in most cases, violent behaviours occur without warning signs (Cooper et al. 1983; Hughes 1996; Buchanan and Leese 2001; Ilkiw-Lavalle and Grenyer 2003; Duxbury and Whittington 2005), some authors have suggested that aggressive and violent episodes could be associated with specific risk factors and preceded by behavioural warning signs (Powell et al. 1994, Sheridan et al. 1990, Lee et al. 1989; Allen et al. 2005). Similarly, Kasper et al. (2013) defined some behavioural warning signs that patients can experience before agitation: hostile mood, tension and aggressive facial expression, increased restlessness, threatening posture and gestures, increased volume in speaking, sudden movements and decreased body distance, verbal threats, prolonged eye contact and physical damage.

A systematic review of 66 studies in unselected psychiatric populations (Cornaggia et al. 2011) found that the variables most frequently associated with aggression/violence in psychiatric wards were the occurrence of previous aggression/violence episodes, the presence of impulsiveness/hostility, disturbing clinical symptoms, provocative situations, verbally demeaning or hostile behaviour, extended length of hospital stay, non-voluntary admission, and aggressor and victim of the same gender (Hankin et al. 2011). Furthermore, some demographic and diagnosis risk factors have been reported such as young age, male gender, not being married, a diagnosis of schizophrenia or bipolar disorder (specially when positive psychotic symptoms and/or comorbidity with substance use disorder are present), a greater number of previous admissions, a history of self-destructive behaviour, a history of suicidal attempts and a history of substance use (Långström et al. 2009; Dack et al. 2013; Nourse et al. 2014; Popovic et al. 2015).

In this context, different assessment tools have been designed to evaluate the risk for aggression/violence using a variety of demographic/personal history, clinical, situational, and clinician variables as indicators of the short-term risk of aggression/violence (Doyle and Dolan 2006; Linaker and Busch-Iversen 1995; McNiel and Binder 1994; Ogloff and Daffern 2006).

A systematic review of the literature identified three observed-rater assessment tools developed to identify risk of aggression/violence in agitated psychiatric patients (Table 3). The Broset Violence Checklist (BVC) has been developed as a predictive tool of a violent episode in the next 24 h in psychiatric inpatients (Linaker and Busch-Iversen 1995; Almvik and Woods 1999). The BVC measures 6 items: confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects. The Historical Clinical Risk Management-20 (HCR-20) allows clinicians to evaluate 20 items of aggression/violence potential (Webster et al. 1997). It was found to be effective in predicting violent behaviour in clinical psychiatric, forensic, and correctional settings as well as among subjects undergoing acute episodes of major mental disorder (Ogloff and Daffern, 2006; Dolan and Blattner al. 2010). The McNiel-Binder Violence Screening Checklist (VSC) was initially designed to assess the short-term risk of aggression/violence among mentally ill patients acutely admitted to short-term inpatient units. This is a five-item scale that includes clinical, historical, and demographic factors. McNiel and Binder (1994) validated this scale in a sample of hospitalised acute psychiatric patients with multiple diagnoses. This instrument has been found to have moderate sensitivity (57.2%) and specificity (70.0%) for predicting violence in patients admitted to a psychiatric

inpatient unit when compared with the Brief Psychiatric Rating Scale (BPRS) and Overt Aggression Scale (OAS) (McNiel and Binder 1994).

## Management

Agitation requires prompt and safe intervention. Traditional methods for treating agitated patients, i.e., routine physical restraints and involuntary medication, have been progressively replaced by non-coercive approaches (Richmond et al. 2012). Non-pharmacological methods of behaviour control, such as verbal de-escalation, or even nicotine replacement therapy, may also be helpful in the initial management of the agitated patient (Hill and Petit 2000; Marder 2006). In addition, pharmacological strategies have evolved in the past years with the introduction of better tolerated non-oral pharmacological options and a wide choice of new patient-friendly oral and inhaled formulations (Baker 2012; Popovic et al. 2015).

In general, the available literature has classified four approaches for the management of the agitated patient that are neither mutually exclusive nor absolute in their order of implementation: environmental manipulation, de-escalation techniques, physical/mechanical restraint or seclusion and pharmacological interventions (Petit 2005). The *Project BETA*, performed a list of six goals to be considered for the management of agitation in the emergency psychiatric care (Table 4) (Zeller and Rhoades 2010).

There is a lack of controlled studies comparing different non-pharmacological interventions. For this reason, information regarding non-pharmacological interventions mainly comes from recommendations and expert consensus. The literature search retrieved 102 citations concerning non-pharmacological interventions, of which 82 have been excluded because of low quality evidence or non-target populations. Twenty remaining citations were reviewed.

## Non-pharmacological interventions

**Environmental modifications and safety concerns.** The initial concern in the management of agitation should be the safety of the patient and those

nearby in the context of the physical environment (Schleifer 2011). Primarily, physicians and/or any other staff member should never put themselves in an unsafe situation (e.g., in a closed room or where access to doors is blocked or other compromising locations). All items or objects that can be potentially dangerous should be removed. It is also important to maintain a safe distance from an agitated patient and to respect the patient's personal space. Prolonged or intense direct eye contact can be perceived as menacing by the patient. Body language and positions can also be considered confrontational and threatening (e.g., crossed arms or hands behind the back or hidden). It is recommended that agitated patients should not be visited by a single interviewer (Petit 2005; Ramadan 2006),

In order to provide some recommendations, Marder (2006), described some appropriate environmental modifications such as: assuring that the patient is physically comfortable, decreasing external stimuli through the use of relative isolation (a quiet room or an individual examination room), minimising waiting time, communicating a safe, respectful and caring attitude, removing all potentially dangerous objects and monitoring the way in which staff members approach the patient. The project BETA workgroup also provided guidance that pointed both the need for a physical space designed for safety (e.g. moveable furniture, two exit doors, minimisation of sensory stimulation, and monitorization of objects that may be used as weapons) as well as an adequate number of trained staff in verbal de-escalation techniques (Richmond et al. 2012).

**Verbal de-escalation.** Verbal de-escalation was initially defined by Stevenson and Otto (1998) as "talking the patient down", describing it as a complex and interactive process in which a patient is redirected towards a more peaceful personal space. Verbal de-escalation techniques have shown the potential to decrease agitation and reduce the risk of associated violence. However, while much has been written on the pharmacological approaches to agitated patients, there is still relatively little evidence about the efficacy of verbal techniques (Richmond et al. 2012).

Allen et al. (2001), recommend verbal intervention or voluntary medication (medication given with the patient's consent) before moving to more intrusive strategies. The NICE guidelines on managing short-term violent/disturbed behaviour in inpatient and emergency department settings (*National Institute for Health and Clinical Excellence* 2005) also described de-escalation as the use of various psychosocial short-term techniques aimed to calm disruptive behaviours and prevent

Table 4. The six goals of emergency psychiatric care.

- (1) Exclude medical causes of symptoms
- (2) Rapidly stabilise the acute crisis
- (3) Avoid coercion
- (4) Treat in the least restrictive setting
- (5) Form a therapeutic alliance
- (6) Ensure an appropriate disposition and after-care plan

Adapted from Zeller (2010).

disturbed/violent behaviours. These guidelines emphasise the need to observe for warning signs of anger and agitation, approaching the patient in a calm controlled manner, giving choices and maintaining the patient's dignity. More recently, the *project BETA* has proposed 10 domains of verbal de-escalation techniques for the management of the agitated patient (Fishkind 2002; Richmond et al. 2012) (Table 5). The authors considered non-coercive de-escalation techniques as the intervention of choice in the management of acute agitation in order to calm the agitated patient by gaining his/her cooperation (Knox and Holloman 2012).

**Physical restraint and seclusion.** Physical or mechanical restraint and seclusion are interventions traditionally used for the treatment and management of disruptive and violent behaviours in psychiatry (APA 1987). Restraint involves measures designed to confine the patient's body movements and seclusion is the placement and retention of the patient in a bare room for containing the escalating clinical situation (Gutheil 1980).

There is much controversy regarding the use of restraints and seclusion for the agitated patient and these interventions may have deleterious physical and psychological effects both in agitated patients and the clinical staff (Fisher 1994). Hankin et al. (2011) have also questioned the use of coercive measures (physical restraint, chemical restraint and seclusion) due to their dubiously therapeutic efficacy, their often inappropriate use, and the potential negative effects on patients, staff, and the therapeutic relationship they can have. Such concerns arise because of reports of death or physical injury occurring following restraint (Mohr et al. 2003). It has been argued that the cascade of physiological responses associated with states of emotional hyperarousal may compromise restrained patients physically and that asphyxia, cardiac complications, drug overdoses or interactions, blunt trauma, strangulation or choking, fire or smoke inhalation, and aspiration have all been reported following restraint (Mohr et al. 2003). Such concerns have led to the Joint Commission on

Accreditation of Healthcare Organisations (JCAHO) (The Joint Commission 2000) recommending that these interventions should only be used in an emergency clinical situation when other attempts to manage agitation have failed and there is imminent risk of harm to a patient or others. According to this, it has been also suggested that a good knowledge of each county regulatory policies should be attempted when restraints and seclusion are performed (Jarema 2015).

Donat (2003) reviewed several initiatives aimed at the reduction of seclusion and restraint in a public psychiatric hospital and reported that 75% of the decrease in using these techniques over 5 years was associated with an early identification scheme of patients at risk of agitation. There is a lack of data regarding other methods aimed at reducing the need for restraint and seclusion. Generally, it is recommended that all clinical staff in emergency departments or acute psychiatric settings should be trained in verbal de-escalation techniques and in the prevention and management of agitated and aggressive behaviour (Knox and Holloman 2012).

However, as the *project BETA* consensus guidelines (Knox and Holloman 2012) suggest, there may be clinical situations in which verbal and behavioural techniques are not effective and the use of restraint and/or seclusion becomes necessary to prevent harm to the patient and/or staff. If this is needed, it should be always used for the shortest period of time possible, and never as a means of punishment, for the convenience of staff, or as a substitute of a treatment programme (Petit 2005; Marder 2006). In addition, once the decision to proceed with restraint or seclusion has been made, there should be sufficient trained staff available so that the procedure can be performed safely and effectively. The *BETA* consensus guidelines recommend that if a patient is in immediate danger to him/herself or others restraint is indicated, if the patient is not a danger to others, seclusion might be sufficient. However, if the patient becomes a danger to him/herself while in seclusion, restraint may be appropriate (Knox and Holloman 2012). Even when a patient is restrained, efforts in verbal de-escalation should continue. Either way, medication should be administered to calm a patient who has been placed in restraint. It is also essential that all patients in restraint or seclusion must be monitored to assess response to medication and to prevent complications. All staff members in emergency departments and acute psychiatric settings should be familiar with the types of restraint used in their programmes and how they should be appropriately applied, monitored, and how to assess potential bodily injury that might result from application of the restraint. Video cameras in

Table 5. Principles of de-escalation techniques.

- (1) Respect personal and space
- (2) Do not be provocative
- (3) Establish verbal contact
- (4) Be concise
- (5) Identify wants and feelings
- (6) Listen closely to what the patients is saying
- (7) Agree or agree to disagree
- (8) Lay down the law and set clear limits
- (9) Offer choices and optimism
- (10) Debrief the patient and staff

Adapted from Fishkind (2002) and Richmond et al. (2012).

clinical areas can be used in an instructive manner to review the restraint or seclusion episode in order to verify if other, less forceful, interventions could have been tried. There is also a need for guidelines on the use of such strategies incorporated into the programme's policies and procedures.

### **Pharmacological intervention**

In patients for whom non-pharmacological treatments fail or are not indicated, medication can be an effective treatment strategy for acute agitation (Baker 2012). It has been described that the ideal medication for the acute management of agitated patients should be easy to administer and none traumatic; provide rapid tranquilisation without excessive sedation; have a fast onset of action and a sufficient duration of action; and have a low risk for significant adverse events and drug interactions (Allen et al. 2003; Ng and Zeller 2010; Zimbroff et al. 2007).

The pharmacological management of acute agitation has traditionally employed three classes of medications: first generation antipsychotics (FGA), benzodiazepines (BZDs), and second generation antipsychotics (SGA) (Marder 2006). During the last few years, treatment options have grown with the development of new intramuscular (i.m.) SGA and different novel patient friendly oral, sublingual, and inhaled formulations (Baker 2012; Jarema 2015; Popovic et al. 2015). Possibly due to the long tradition of its use, haloperidol is still extensively used in psychomotor agitation, despite these new formulations and although the sole use of haloperidol has been discouraged in a recent Cochrane review of this FGA for psychosis-induced aggression and agitation (Powney et al. 2012). Nevertheless, none of the current pharmacological options fulfil all of the criteria for an ideal anti-agitation medication, thus there is still a need for new pharmacological options (Ng and Zeller 2010).

The literature search of clinical trials of pharmacotherapy for agitation in the psychiatric settings retrieved 589 citations. After the evaluation of the abstracts and/or full texts of these citations, 74 clinical trials and studies were included in this consensus.

**Oral formulations.** Despite the limitations of a slow onset of action (Citrome 2004; Ng and Zeller 2010) and patients "cheeking" oral tablets (taking, but not swallowing) (Zimbroff et al. 2007), oral formulations are generally preferred over i.m. preparations as initial treatment of agitated patients (Wilson et al. 2012). Alternative routes that have been recently developed, such as oral rapidly dissolving tablets, sublingual formulations and aerosolized inhaled formulations

(Nordstrom et al. 2012), will be described in a separate section. Table 6 shows the main results of the available studies.

**Benzodiazepines (BZDs).** The literature search on oral BZDs in monotherapy did not retrieve any result for controlled trials. The only study found assessing the efficacy of oral adjunctive BZDs for agitation is a trial in which risperidone oral solution (OS) (2–6 mg/day) plus oral clonazepam (0–8 mg/day) was compared with i.m. haloperidol (10–20 mg/day) (alone or plus BZDs) over the course of 6 weeks in a sample of 205 agitated schizophrenic patients (Fang et al. 2012). In this randomised, open-label, two-phase trial, the oral combination treatment was as effective as i.m. haloperidol in reducing the Positive and Negative Syndrome Score – Excited Component (PANSS-EC) scores except at 4 h when i.m. haloperidol was superior ( $P=0.025$ ).

**Antipsychotics.** Antipsychotics have been extensively used for the treatment of acute agitation. Amongst these, SGAs have been recently recommended over haloperidol either alone or in combination for agitation due to a psychiatric illness (Wilson et al. 2012; Kasper et al. 2013).

The literature search identified 26 trials regarding oral antipsychotics for the pharmacological treatment of agitation: one assessing oral FGA, four comparing FGA with SGA and 21 assessing SGA.

**First generation antipsychotics (FGAs).** Low potency oral FGAs have not been studied in randomised, double-blind, controlled trials (Stabenau and Grinols 1964; Herrera et al. 1988; Chan et al. 2014). One open-label trial compared oral haloperidol in monotherapy with the combination of oral haloperidol plus oral levomepromazine for agitation in schizophrenic patients. In this 8-week, open-label trial, 19 inpatients were recruited: 10 given monotherapy and nine the combination treatment. The reduction in agitation on the Brief Psychiatric Rating Scale (BPRS) agitation subscale was greater for the combination therapy compared to the monotherapy group at weeks 1 ( $P=0.005$ ) and 2 ( $P=0.01$ ). Additionally, there were no significant effects of treatment on any of the safety measures according to the ECG, blood pressure or heart rate (Higashima et al. 2004).

### **Second generation antipsychotics (SGAs)**

**Olanzapine.** Amongst oral SGAs, olanzapine is the best-studied medication for psychiatric agitation. The first trial reported in the literature was performed by Kinon et al. (2001). In this 6-week, multisite, randomised,

Table 6. Included studies of oral medications for the management of agitation.

Study	Design	Population	Interventions	Agitation outcomes
Kinon et al. (2001)	RCT, double-blind, prospective, multisite. 3 weeks.	N = 100. Acute agitation in schizophrenia, schizophreniform or schizoaffective disorders. Inpatients.	(1) Olanzapine p.o. 5–20 mg/day (n = 52) (2) Haloperidol p.o. 5–20 mg/day (n = 48)	BPRS agitation score and BPRS positive symptom score: Improvement in olanzapine group significantly greater than in haloperidol group (P < 0.0002).
Currier and Simpson (2001)	RCT.	N = 60. Agitation in psychosis. Emergency department	(1) Risperidone OS (2 mg) plus lorazepam i.m. (2 mg) (n = 30) (2) Haloperidol i.m. plus lorazepam i.m. (n = 30)	PANSS-EC, CGI, and time to sedation: Both treatment groups improve but no differences between them were found.
Baker et al. (2003)	RCT, double-blind. 4 days.	N = 148. Agitated patients with schizophrenia, schizoaffective or schizophreniform disorder, or bipolar I disorder (manic or mixed episode).	(1) Olanzapine po flexibly dosed as needed (up to 40 mg/day) plus lorazepam i.m. as needed (2) Olanzapine 10 mg/day plus lorazepam i.m. as needed	PANSS-EC at 24 h: Significant decreases in both treatment groups (P < 0.001), with statistically significant greater improvement the flexible dosage group (P = 0.006).
Chengappa et al. (2003)	RCT, double-blind, placebo controlled, multisite. 6 weeks.	N = 257. Agitation in schizophrenia.	(1) Quetiapine p.o. 150, 300, 600, 750 mg (n = 175) (2) Haloperidol p.o. 12 mg (n = 42) (3) Placebo po (n = 40)	BPRS agitation scores: Quetiapine treatment group reduced agitation scores significantly compared with placebo, but not statistically significant compared with haloperidol.
Yatham et al. (2003)	RCT, double-blind, parallel-group, placebo-controlled, multisite. 6 weeks.	N = 232. Agitation in bipolar I disorder. Inpatients.	(1) Quetiapine po plus lithium/divalproex p.o. (n = 116) (2) Placebo p.o. plus lithium/divalproex p.o. (n = 116)	PANSS Activation and PANSS Supplemental Aggression Risk subscale: PANSS Activation was not significantly different in both treatment groups. PANSS Supplemental Aggression Risk subscale scores significantly improved at Day 21 in the QTP plus Li/DVP group vs. placebo plus Li/DVP (P < 0.05).
Kinon et al. (2004)	RCT, double-blind, prospective. 3 weeks.	N = 100. Acutely agitated patients with schizophrenia or schizophreniform or schizoaffective disorder. Inpatients.	(1) Olanzapine p.o. 10 mg/day plus lorazepam as needed (n = 52) (2) Haloperidol p.o. 10 mg/day plus lorazepam as needed (n = 48)	PANSS Agitation subscale scores from 1 to 24 h: Significant improvement at all time points (P < 0.001) with no significant differences between treatment groups.
Currier et al. (2004)	RCT, single-blind, prospective, parallel-group, multisite, non-inferiority. 24 h.	N = 162. Psychotic agitation in schizophrenia or schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorders.	(1) Risperidone p.o. 2 mg/day (n = 83) (2) Haloperidol i.m. 5 mg/day (n = 79)	PANSS-EC at 30, 60, 120 min: Both agents significantly improved (P < 0.001), with no significant difference between groups.
Higashima et al. (2004)	RCT, OL. 8 weeks.	N = 19. Agitation in schizophrenia. Inpatients.	(1) Haloperidol p.o. (n = 10) (2) Haloperidol p.o. plus levomepromazine p.o. (n = 9)	BPRS- agitation subscale: Combination therapy group improves significantly compared with the monotherapy group.
Sachs et al. (2004)	RCT, double-blind, parallel-group, placebo-controlled, multisite. 3 weeks.	N = 170. Agitation in bipolar I disorder. Inpatients.	(1) Quetiapine p.o. plus lithium/divalproex p.o. (n = 81) (2) Placebo p.o. plus lithium/divalproex p.o. (n = 89)	PANSS Activation and PANSS Supplemental Aggression Risk subscale: PANSS Activation was not significantly different in both treatment groups. PANSS Supplemental Aggression Risk subscale scores significantly improved at Day 21 in the QTP plus Li/DVP group vs. PBO plus Li/DVP (P < 0.05).
McIntyre et al. (2005)	RCT, double-blind, placebo-controlled, multisite. 12 week.	N = 299. Agitation in bipolar I mania. Inpatients.	(1) Quetiapine p.o. (up to 800 mg/day) (n = 102) (2) Placebo p.o. (n = 100)	PANSS agitation subscale: Quetiapine improved significantly compared with placebo.

(continued)

Table 6. Continued

Study	Design	Population	Interventions	Agitation outcomes
Bowden et al. (2005)	RCT, double-blind, placebo-controlled, multisite, 12 week.	N = 302. Agitation in bipolar I mania.	(3) Haloperidol p.o. (up to 8 mg/day) (n = 98) (1) Quetiapine p.o. (up to 800 mg/day) (n = 107) (2) Placebo p.o. (n = 95) (3) Lithium p.o. (n = 98)	PANSS agitation subscale: Quetiapine improved significantly compared with placebo.
Veser et al. (2006)	RCT, double-blind, placebo-controlled, 90 min.	N = 30. Agitated patients with psychosis. Medical emergency department.	(1) Risperidone p.o. 2 mg/day plus lorazepam i.m. 2 mg/day (n = 10) (2) Haloperidol p.o. 5 mg/day plus lorazepam i.m. 2 mg/(n = 10) (3) Placebo p.o. plus lorazepam i.m. 2 mg/day (n = 10)	PANSS total scores at 30 and 90 min: No significant differences between treatment groups.
Normann et al. (2006)	OL, Multisite, 7 days.	N = 191. Agitation in schizophrenia. Inpatient.	(1) Risperidone ODT 1–8 mg	PANSS total and CGI-S at 7 days: Significant improvement ( $P < 0.0001$ )
Marder et al. (2007)	4 RCT, double-blind, placebo-controlled, 4–6 weeks.	N = 1187. Acute agitation in schizophrenia.	(1) Aripiprazole p.o. 10 mg/day (2) Aripiprazole p.o. 15 mg/day (3) Aripiprazole p.o. 20 mg/day (4) Aripiprazole p.o. 30 mg/day (5) Placebo	PANSS total, CGI-I, and PANSS-EC. All aripiprazole groups significantly improved symptoms of acute schizophrenia regardless of baseline level of agitation at weeks 2 to 6, compared with placebo ( $P < 0.05$ ).
Villari et al. (2008)	RCT, Single-blinded, Prospective, 72 h.	N = 101. Agitation in psychosis. Psychiatric emergency service.	(1) Haloperidol p.o. 5–15 mg/day (n = 28) (2) Risperidone p.o. 2–6 mg/day (n = 27) (3) Olanzapine p.o. 10–20 mg/day (n = 24) (4) Quetiapine p.o. 300–800 mg/day (n = 22)	MOAS and the hostility-suspiciousness factor derived from BPRS: Improvement in all treatment groups with no differences between groups.
Kinon et al. (2008)	RCT, double-blind, parallel-group, 5 days.	N = 604. Agitation in schizophrenia or schizophreniform or schizoaffective disorder. Inpatients.	(1) Olanzapine p.o. 20 mg/day (plus lorazepam i.m. as needed) (n = 306) (2) Aripiprazole p.o. 15–30 mg/day (plus lorazepam i.m. as needed) (n = 298)	PANSS-EC scores from baseline to the end of each day: Both treatment groups significantly improved ( $P < 0.001$ ) but with no differences between them.
Hatta et al. (2008)	Pseudo-randomised, OL, multisite, 12 h.	N = 87. Agitation in psychosis. Psychiatric emergency service.	(1) Risperidone ODT 3 mg (n = 54) (2) Olanzapine ODT 10 mg (n = 34)	PANSS-EC at 60 min: Significant improvement in all treatment groups ( $P < 0.0001$ ) with no differences between groups ( $P = 0.09$ ).
Escobar (2008)	Observational, Multisite.	N = 278. Agitation in psychotic patients (77% schizophrenia, 12.2% bipolar disorder). Psychiatric emergency service.	(1) Olanzapine p.o. (n = 148) (2) Olanzapine p.o. plus other antipsychotic (n = 15) (3) Other antipsychotics p.o. (n = 115)	PANSS-EC, CGI-S and ACES at baseline, before any re-intervention (if needed) and at discharge: All treatment groups improved significantly ( $P < 0.001$ ) all agitation measures.
Hsu et al. (2010)	RCT, single-blind, prospective, multisite, 24 h.	N = 42. Agitation in psychosis (schizophrenia, bipolar I disorder, schizoaffective disorder, delusional disorder, or other psychotic disorders). Inpatients.	(1) Olanzapine i.m. 10 mg (n = 11) (2) Haloperidol i.m. 7.5 mg (n = 11) (3) Olanzapine ODT 10 mg (n = 10) (4) Risperidone OS 3 mg (n = 10)	PANSS-EC: Both olanzapine treatment groups presented significant decreases before 90 min post-treatment compared with the haloperidol and risperidone group.
Lim et al. (2010)	RCT, OL, single-blind, 24 h.	N = 124. Agitation in psychosis (schizophrenia, schizoaffective disorder, delusional disorder, bipolar I disorder). Emergency department and inpatients.	(1) Risperidone ODT 2–6 mg (n = 62) (2) Haloperidol i.m. 5–15 mg (n = 62)	PANSS-EC and CGI-S at 2, 6, 24 h: Both scores were significantly decreased over time ( $P < 0.0001$ ) without any significant group difference.

(continued)

Table 6. Continued

Study	Design	Population	Interventions	Agitation outcomes
Fang et al. (2012)	RCT, OL, parallel-group. Multisite. 5 days.	N = 205. Agitation in schizophrenia and schizoaffective disorder. Inpatients.	(1) Risperidone p.o. 2–6 ml/day ± clonazepam p.o. 0–8 mg/day (n = 104) (2) Haloperidol i.m. 10–20 mg/day (n = 101)	PANSS-EC at 2, 4, 24 h: Significant improvement in both treatment groups ( $P > 0.05$ ) but with no differences between them ( $P < 0.01$ ). PANSS psychotic agitation at 2 h: Significant improvement in the asenapine group compared with the placebo group.
Pratts et al. (2014)	RCT, double-blind. 2h.	N = 120. Psychiatric agitation. Psychiatric emergency service.	(1) Asenapine sl 10 mg (n = 60) (2) Placebo (n = 60)	PANSS psychotic agitation at 2 h: All drugs presented significant improvement ( $P < 0.001$ ), but none was superior.
Walther et al. (2014)	Randomised, single-blind. 5 days.	N = 43. Severe agitation in schizophrenia or schizophreniform or schizoaffective disorder. Acute care psychiatric units.	(1) Haloperidol p.o. 15 mg (n = 14) (2) Olanzapine p.o. 10 mg (n = 15) (3) Risperidone p.o. 2–6 mg (n = 14)	

OL, Open Label; RCT, Randomised Controlled Trial; p.o., oral; i.m., intramuscular; ODT, oro-dispersible tablets; OS, oral solution; ACES, Agitation and Calmness Evaluation Scale; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; MOAS, Modified Overt Aggression Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale – Excited Component; QIP, quetiapine; Li/DVP, lithium/divalproex.

double-blind trial in acutely agitated inpatients with schizophrenia, schizophreniform or schizoaffective disorders treated with oral haloperidol (5–20 mg/day) or oral olanzapine (5–20 mg/day), the olanzapine group experienced a significant greater improvement in agitation compared to the haloperidol group ( $P < 0.0002$ ), according to the BPRS agitation subscale score, at weeks 4, 5 and 6 (Kinson et al. 2001). Based on these results, the authors suggested that oral olanzapine might be considered a first-line treatment in agitated psychiatric patients. Later, the same authors performed a 3-week, randomised, double-blind trial of oral olanzapine (10 mg/day) compared to oral haloperidol (10 mg/day) in 57 acutely agitated patients with schizophrenia, schizophreniform or schizoaffective disorder (Kinson et al. 2004). Both treatment groups experienced a significant improvement in the PANSS agitation subscale scores ( $P < 0.001$ ) with no significant differences between groups in reducing acute agitation. Fewer patients in the olanzapine group presented treatment-emergent adverse events (AEs) compared with the haloperidol group (67.3 vs. 85.4%;  $P = 0.038$ ). More recently, a 5-day, randomised, double-blind, parallel-study compared oral olanzapine (20 mg/day) with oral aripiprazole (15–30 mg/day) in 604 agitated inpatients with schizophrenia, schizophreniform or schizoaffective disorder (Kinson et al. 2008). Both agents significantly decreased the PANSS-EC scores from baseline to the end of each day ( $P < 0.001$ ), with no significant differences between the two drugs in terms of efficacy. However, the olanzapine group showed a significantly greater increase in fasting triglycerides ( $P < 0.001$ ), glucose ( $P = 0.030$ ) and prolactin levels ( $P < 0.001$ ) compared with the aripiprazole group.

Baker et al. (2003) conducted a 4-day, randomised, double-blind trial where flexible doses of oral olanzapine (up to 40 mg/day) were compared with a fixed oral dose of olanzapine (10 mg/day, plus i.m. lorazepam 4 mg/day as needed) in 148 acutely agitated patients with schizophrenia, schizoaffective or schizophreniform, or bipolar I disorder (manic or mixed episode). Both olanzapine doses (flexible and fixed) were associated with significant decreases in the PANSS-EC scores at 24 h ( $P < 0.001$ ), with greater improvement in the flexible dose group compared with the fixed dose group ( $P = 0.006$ ). Both dose treatments were well tolerated, with no clinically significant differences in the most common AE (somnolence) for both treatment groups. Although the onset of action was not captured in the study, the authors stated that the flexible dose group was more effective in controlling agitation rapidly without over-sedation (Baker et al. 2003).

Some observational studies have also reported greater effectiveness of oral olanzapine compared to

several other oral FGAs, and SGAs or BZDs (Escobar 2008). In this observational, multisite study of 278 psychotic agitated patients, oral olanzapine in monotherapy ( $n=148$ ; 53.2%) significantly improved the severity of agitation compared to baseline ( $P<0.001$ ) when measured with the PANSS-EC, the CGI-S and the Agitation-Calmness Evaluating Scale (ACES) (Escobar 2008). Patients in the olanzapine group reported no significant AEs during the course of the study.

The efficacy and tolerability of olanzapine orodispersible tablets (ODT) have been also compared with risperidone oral solution (OS) in a pseudorandomized, open-label, flexible-dose, multisite study in acute psychotic agitation ( $n=87$ ) (Hatta et al. 2008). In this trial, the two drugs were equally effective in reducing agitation according to the PANSS-EC scores ( $P<0.0001$ ). No differences were found amongst the two drugs regarding the number of patients needing additional treatment due to worsening (olanzapine ODT, 11.8%; risperidone OS, 9.4%). No differences in vital signs were found except at 60 min, where the mean change heart rate in the olanzapine ODT group was significantly greater than that in the risperidone OS group ( $P=0.03$ ). No significant differences were seen in the rate of extrapyramidal symptoms (EPS). Later, Hsu et al. (2010) compared olanzapine ODT (10 mg,  $n=10$ ), i.m. olanzapine (10 mg,  $n=11$ ), i.m. haloperidol (7.5 mg,  $n=11$ ), and risperidone OS (3 mg,  $n=10$ ), in 42 agitated psychotic inpatients. In this 24-h, multisite, randomised, single-blind trial, olanzapine ODT and i.m. olanzapine were more effective than i.m. haloperidol within 90 min after initiation of the treatment according to the PANSS-EC scores. Drowsiness was the most common AE reported in all treatment groups, but the difference between them was not significant.

**Risperidone.** The effectiveness and safety of risperidone ODT was evaluated in a multisite, open-label, observational trial in 191 acutely agitated schizophrenic inpatients, showing a significant reduction in the PANSS total scores and in the CGI-S scores after 7 days of treatment and in the PANSS item 4 (excitation) after 2 h of the first dose of risperidone ODT (Normann et al. 2006). AEs were reported in 61 patients, with the EPS (6.8%) being the most common. When risperidone OS has been compared with olanzapine ODT, both treatments resulted as equally effective in the management of agitation in psychotic patients in a pseudo-randomised, open-label study (Hatta et al. 2008). A 24-h, randomised, open-label, and single-blind study compared risperidone ODT (2–6 mg;  $n=62$ ) with i.m. haloperidol (5–15 mg;  $n=62$ ) in 124 patients with psychotic agitation recruited from emergency rooms or inpatient

wards (Lim et al. 2010). The authors found a significant reduction of the PANSS-EC and CGI-S scores over time in both treatment groups without any significant difference at 2, 6 and 24 h. There were also no differences in safety parameters between the two treatment arms. In another randomised single blind trial, risperidone OS was as effective as i.m. haloperidol, but inferior to olanzapine ODT and i.m. olanzapine according to the PANSS-EC scores in agitated psychotic patients (Hsu et al. 2010)

Regarding oral risperidone in combination with i.m. BZDs, the literature reported four trials comparing the efficacy of this combination with i.m. haloperidol (alone or *plus* BZDs). Firstly, risperidone OS (2 mg) *plus* i.m. lorazepam (2 mg) was compared with i.m. haloperidol *plus* i.m. lorazepam in 60 psychotic agitated patients in an emergency department (Currier and Simpson 2001). This study found that risperidone OS was as effective as the i.m. haloperidol when measured by the PANSS agitation subscales, the CGI scale, and by the time to calming. No AEs were recorded for patients in the risperidone OS arm. The same research group conducted a 24-h, multisite, randomised, single-blind, non-inferiority trial comparing oral risperidone (2 mg;  $n=83$ ) and i.m. haloperidol (5 mg;  $n=79$ ), both in combination with i.m. lorazepam (2 mg), in 162 patients with psychotic agitation (schizophrenia, schizoaffective disorder, mania, acute paranoid reaction, or delusional disorders) (Currier et al. 2004). Both treatment groups significantly improved in the PANSS-EC scores at 30, 60 and 120 min after treatment ( $P<0.001$ ), with no significant differences between them. Consequently, the authors concluded that a single oral dose of oral risperidone *plus* lorazepam was as effective and well tolerated as i.m. haloperidol *plus* lorazepam for the rapid control of psychotic agitation. In another double-blind, placebo-controlled trial, oral risperidone (2 mg) *plus* i.m. lorazepam (2 mg) was compared to i.m. haloperidol 5 mg *plus* i.m. lorazepam (2 mg) and to oral placebo *plus* i.m. lorazepam (2 mg) in 30 psychotic agitated patients (Veser et al. 2006). No differences were found between risperidone and haloperidol treatment groups in reducing agitation and psychosis according to the PANSS-EC total scores at 30 and 90 min after dosing.

As described before, a 5-day, multisite, randomised, parallel-group, open-label study compared oral risperidone (2–6 ml/day) *plus* oral clonazepam (0–8 mg/day) with i.m. haloperidol (10–20 mg/day) in a sample of 205 agitated schizophrenic patients (Fang et al. 2012). Significant improvements on the PANSS-EC were seen in both treatment groups ( $P<0.01$ ) with no statistically significant differences in the mean change of the PANSS-EC scores, except at 4 h with greater reductions in the

i.m. treatment group ( $P=0.025$ ). Not only that the oral treatment was better tolerated than the i.m. haloperidol ( $P<0.001$ ) in terms of overall AE, oral risperidone *plus* oral clonazepam also had similar therapeutic effects as i.m. haloperidol in those patients (Fang et al., 2012).

**Aripiprazole.** A post hoc analysis of four randomised, double-blind, placebo-controlled studies that evaluated the efficacy and safety of oral aripiprazole for the treatment of patients with acute exacerbations of schizophrenia (Daniel et al. 2000; Kane et al. 2002; Potkin et al. 2003; McEvoy et al. 2007), was performed by Marder et al. (2007). In this, oral aripiprazole (10, 15, 20 or 30 mg/day;  $n=790$ ) and placebo ( $n=397$ ) were analysed in terms of agitation improvement in a sample of 1187 agitated patients with acute schizophrenia. According to the PANSS total score, the CGI-I, and the PANSS-EC scores at weeks 2 to 6, aripiprazole was significantly superior in the improvement of symptoms of agitation with lower scores in those scales ( $P<0.05$ , for each measure). Additionally, AEs were reported as generally mild across groups.

A randomised, double-blind, parallel-study of oral olanzapine vs. oral aripiprazole in 604 psychotic agitated inpatients did not report clinical differences in the improvement of agitation (PANSS-EC) between both treatments groups. However, aripiprazole treatment was associated with a better glucose, triglyceride and prolactin profile compared with olanzapine (Kinon et al. 2008).

**Quetiapine.** Chengappa et al. (2003) performed a secondary analysis of a previous trial that compared 5 doses of quetiapine (150, 300, 600 and 750 mg) with haloperidol (12 mg) and placebo in a 6-week, multisite, double-blind, randomised, placebo-controlled trial in 257 acutely schizophrenic patients (Arvanitis and Miller 1997). This post hoc analysis found that quetiapine significantly reduced agitation scores (derived from the BPRS) compared to placebo, but this difference was not statistically significant compared to haloperidol.

Quetiapine for treating agitation was also assessed in a combined analysis (Vieta et al. 2005) of data from two 12-week, randomised, double-blind, placebo-controlled trials in patients with bipolar I mania (Bowden et al. 2005; McIntyre et al. 2005). In both trials, patients were allocated to receive quetiapine (up to 800 mg/day;  $n=208$ ) or placebo ( $n=195$ ) with significant improvements in aggression and agitation (PANSS agitation subscale scores) in the quetiapine treatment group relative to placebo. Quetiapine was generally well tolerated in comparison with placebo, but AEs such as somnolence, dry mouth, weight gain and dizziness

occurred with a significantly greater incidence vs. placebo. Another analysis (Yatham et al. 2004) evaluated the use of quetiapine in agitation based upon two double-blind, placebo-controlled trials (Yatham et al. 2003; Sachs et al. 2004). These studies were initially performed to assess the effectiveness of quetiapine in the treatment of bipolar mania. A sample of 402 bipolar I manic patients was randomised to receive either quetiapine in combination with lithium/divalproex ( $n=197$ ) or placebo *plus* lithium/divalproex ( $n=205$ ) for 3 or 6 weeks. No significant differences were found between the two treatment groups in the PANSS Activation subscales scores. However, there was a significant improvement from baseline compared with the placebo combination group in the PANSS Supplemental Aggression Risk subscale at day 21 in patients treated with adjunctive quetiapine ( $P<0.05$ ). In addition, AEs were more frequently reported with quetiapine combination than placebo combination, with no significant differences between the two treatment groups.

**First generation antipsychotics (FGAs) vs. second generation antipsychotics (SGAs).** The literature search found five studies comparing the effectiveness of oral FGAs vs. different SGAs (Kinon et al. 2001, 2004; Chengappa et al. 2003; Villari et al. 2008; Walther et al. 2014).

In two double-blind, prospective, multisite trials performed by Kinon et al. (2001, 2004) oral haloperidol was compared to oral olanzapine. The efficacy of olanzapine was superior to haloperidol in the treatment of acutely agitated inpatients with psychosis in the first trial (Kinon et al. 2001) but similar in the second trial in agitated schizophrenic patients (Kinon et al. 2004).

As it was mentioned previously, Chengappa et al. (2003) also found that quetiapine (150, 300, 600 and 750 mg) was as effective as haloperidol (12 mg) in the treatment of agitation in acutely schizophrenic patients.

In a 72-h, randomised, single-blind trial, the effectiveness of oral haloperidol ( $n=28$ ; 5–15 mg/day) was compared with three different oral SGAs: risperidone ( $n=27$ ; 2–6 mg/day), olanzapine ( $n=24$ ; 10–20 mg/day), and quetiapine ( $n=22$ ; 300–800 mg/day) in 101 agitated psychotic patients in a psychiatric emergency service. There were no significant differences between treatment groups regarding primary outcome measures: changes in total scores of the Modified Overt Aggression Scale (MOAS) and the Hostility–suspiciousness factor derived from the BPRS (Villari et al. 2008). Regarding AE, the haloperidol group presented more often with an EPS compared to the other SGA treatment groups

( $P = 0.012$ ). No other differences were found in relation to other AE.

Recently, the efficacy of oral haloperidol (15 mg/day), oral risperidone (2–6 mg/day), and oral olanzapine (20 mg/day) was compared in 43 severely agitated inpatients with schizophrenia, schizophreniform or schizoaffective disorder in a 5-day, randomised, single-blind, controlled study within a naturalistic treatment regimen. All three drugs were equally effective for rapid tranquilisation within 2 h, according to the PANSS psychotic agitation subscale ( $P < 0.001$ ) and no motor AEs differences were found between all treatment groups (Walther et al. 2014).

**Sublingual formulations Asenapine.** Asenapine sublingual tablets is a new SGA option for the treatment of agitation in schizophrenia and acute manic or mixed episodes of bipolar I disorder (Ng and Zeller 2010). There is only one 2-h, randomised, double-blind, controlled trial (Pratts et al. 2014) that compared the efficacy of asenapine (10 mg;  $n = 60$ ) with placebo ( $n = 60$ ) in agitated psychiatric patients. The reduction in the mean PANSS-EC total scores at 2 h was significantly greater in the asenapine group with three requiring treatment. The authors suggested that sublingual asenapine might be effective in the treatment of agitation with an effect size comparable to that observed in prior studies of intramuscular antipsychotics.

**Intramuscular formulations.** Intramuscular formulations provide a more rapid onset of action compared with the oral route of administration, but they could be associated with a higher risk for AE and with patient's reluctance (Ng and Zeller 2010). For the treatment of acute psychotic agitation, parenterally administered antipsychotics or BZDs vs. oral medication offer the advantage of a faster absorption and bioavailability and subsequently a quicker therapeutic response (Currier and Medori 2006; Nordstrom and Allen 2007; Zhang et al. 2013).

Forty-six studies were identified that assessed i.m. administration of antipsychotic agents and/or BZDs (Table 7). Of these, 24 involved FGA, 38 involved SGA and 17 involved BZDs.

**Benzodiazepines (BZDs).** The first randomised, double-blind trial that compared BZDs with FGAs for the management of agitation was performed in 20 manic agitated inpatients treated with lithium. Patients were randomised to i.m. lorazepam vs. i.m. haloperidol and no significant differences in efficacy between groups were found according to the Mania Rating Scale and the BPRS scores. No differences in the AEs profile were found

between the two treatment groups (Lenox et al. 1992). Later, a double-blind randomised clinical trial compared i.m. clonazepam (1–2 mg) vs. i.m. haloperidol (5–10 mg) in 16 agitated psychotic patients with manic-like symptoms (Chouinard et al. 1993). Both medications produced significant reduction of agitation within 2 h of initial treatment, but haloperidol showed a more rapid effect compared with clonazepam. More EPS were also reported in the haloperidol group, but otherwise no differences were found in the AEs profile between the two treatment groups. Battaglia et al. (1997) conducted a 24-h, multisite, randomised, double-blind comparison of i.m. lorazepam (2 mg), i.m. haloperidol (5 mg), and their combination in 98 agitated patients with unspecified psychosis. A reduction in agitation was achieved in all treatment groups from baseline at each hourly evaluation in the Agitated Behaviour Scale (ABS) scores ( $P < 0.01$ ). However, significant ( $P < 0.05$ ) mean differences on the ABS (hour 1) and the modified Brief Psychiatric Rating Scale (MBPRS) (hours 2 and 3) indicated a more rapid tranquilisation in patients receiving the combination treatment. Furthermore, AE profiles did not differ significantly between all treatment groups, although patients receiving haloperidol alone tended to present with more EPS. Another randomised double-blind trial testing the efficacy of i.m. lorazepam vs. the combination of i.m. haloperidol (5 mg) and i.m. lorazepam (2 mg) in managing agitation in a psychiatric emergency setting found a statistically superior efficacy for the combination ( $n = 9$ ) over lorazepam monotherapy ( $n = 11$ ) at 60 min as assessed with the Overt Aggression Scale (OAS), a visual analogue scale (VAS) of agitation and hostility, and the CGI-S scale ( $P < 0.05$ ) (Bieniek et al. 1998). The efficacy of i.m. flunitrazepam (1 mg;  $n = 15$ ) was also compared with i.m. haloperidol (5 mg;  $n = 13$ ) in a 2-h randomised, double-blind trial for the control of agitation in 28 acute psychotic inpatients in emergency psychiatric settings (Dorevitch et al. 1999). Both flunitrazepam and haloperidol exhibited acute anti-agitation effect, as showed by significant reductions in the OAS scores ( $P < 0.001$ ) with no differences between them. The authors also found that within 30 min after treatment initiation, the anti-agitation effect of flunitrazepam was already achieved, whereas the activity of haloperidol increased only gradually ( $P < 0.01$ ). In addition, no AEs differences were found between treatment groups. Although safety was not an outcome parameter of this study, no acute EPS were reported in either group. The TREC (*Tranquilizacao Rapida-Ensaio Clinico* [Rapid Tranquilization Clinical Trial]) Collaborative Group (2003) conducted a 2-week, multisite, randomised, single-blind study of i.m. haloperidol (5–10 mg) plus i.m. promethazine (25–50 mg) vs. i.m. midazolam (15 mg)

Table 7. Included studies of intramuscular medications for the management of agitation.

Study	Design	Population	Interventions	Agitation outcomes
Man and Chen (1973)	RCT, double-blind. 72 h.	N = 30. Agitation in acute exacerbation of chronic psychosis.	(1) Haloperidol i.m. 5–15 mg (n = 15) (2) Chlorpromazine i.m. 50–600 mg (n = 15).	Tranquil at 2 h and need of additional medication: No differences between treatment groups.
Resnick and Burton (1984)	Randomised, double-blind.	N = 27. Agitation and unspecified psychosis.	(1) Droperidol i.m. 5 mg (2) Haloperidol i.m. 5 mg	BPRS at 30 min: Significant reductions in agitation in the haloperidol group compared with the droperidol ( $P < 0.05$ ).
Lenox et al. (1992)	Randomised, double-blind.	N = 20. Agitation in manic episodes. Inpatients.	(1) Lorazepam i.m. (2) Haloperidol i.m.	Mania Rating Scale and BPRS: No differences between treatment groups.
Chouinard et al. (1993)	RCT, double blind.	N = 16. Agitation in psychotic patients with manic-like symptoms.	(1) Clonazepam i.m. 1–2 mg (2) Haloperidol i.m. 5–10 mg	Rapid tranquilisation: Haloperidol group presented results more rapidly than clonazepam group.
Battaglia et al. (1997)	RCT, double-blind, multisite. 24 h.	N = 98. Agitation in unspecified psychosis	(1) Lorazepam i.m. 2 mg (2) Haloperidol i.m. 5 mg (3) Lorazepam i.m. 2 mg plus Haloperidol i.m. 5 mg	ABS score at 1 h: Combination therapy presented greater reductions compared with lorazepam alone but there were no efficacy differences between lorazepam and haloperidol or between haloperidol and combination treatment.
Bieniiek et al. (1998)	RCT, double-blind.	N = 20. Psychiatric emergency setting.	(1) Lorazepam i.m. 2 mg (n = 11) (2) Lorazepam i.m. 2 mg plus Haloperidol i.m. 5 mg (n = 9)	OAS: Combination treatment group resulted superior than lorazepam alone.
Dorevitch et al. (1999)	RCT, double-blind. 2 h.	N = 28. Agitation in psychosis (schizophrenia, schizoaffective disorder, and bipolar disorder). Emergency psychiatric setting.	(1) Flunitrazepam i.m. 1 mg (n = 15) (2) Haloperidol i.m. 5 mg (n = 13)	OAS at 2h: Both treatment groups improved significantly with no differences between groups.
Brook et al. (2000)	Randomised, OL, multisite. 7 day.	N = 132. Agitation in psychosis (schizophrenia, schizoaffective disorder, bipolar disorder, brief psychotic disorder, or psychotic disorder not otherwise specified.) Inpatients.	(1) Ziprasidone i.m. 10–80 mg (n = 90) (2) Haloperidol i.m. 2.5–20 mg (n = 42)	BPRS total score, BPRS agitation items and CGI-S at last assessment: Improved significantly in the ziprasidone group compared with the haloperidol group ( $P < 0.05$ , $P < 0.01$ and $P < 0.01$ , respectively).
Meehan et al. (2001)	RCT, double-blind. 24 h.	N = 201. Agitation in bipolar disorder.	(1) Olanzapine i.m. 10 mg (n = 99) (2) Lorazepam i.m. 2 mg (n = 51) (3) Placebo i.m. (n = 51)	PANSS-EC at 2 h: Olanzapine group improved significantly more than the lorazepam or placebo group.
Lessem et al. (2001)	RCT, double-blind, multisite. 24 h.	N = 117. Acute psychotic agitation.	(1) Ziprasidone i.m. 2 mg (n = 54) (2) Ziprasidone i.m. 10 mg (n = 63)	BARS at 4 h: Ziprasidone 10 mg was significantly more effective than the 2-mg dose ( $P < 0.01$ ).
Daniel et al. (2001)	RCT, double-blind, multisite. 24 h.	N = 79. Agitation in psychosis (schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features or another psychotic disorder).	(1) Ziprasidone i.m. 2 mg (n = 38) (2) Ziprasidone i.m. 20 mg (n = 41)	BARS at 4 h: Ziprasidone 20 mg was significantly more effective than the 2-mg dose group ( $P < 0.001$ ).
Wright et al. (2001)	RCT, double-blind, placebo controlled. 24 h.	N = 311. Agitation in schizophrenia, schizophreniform or schizoaffective disorder.	(1) Olanzapine i.m. 10 mg (2) Haloperidol i.m. 5 mg (3) Placebo i.m.	PANSS-EC at 2 h: Olanzapine group presented significantly improvement from 15 to 45 min compared with haloperidol ( $P < 0.01$ ).
Currier and Simpson (2001)	RCT.	N = 60. Agitation in psychosis. Emergency department	(1) Risperidone OS (2 mg) plus lorazepam i.m. (2 mg) (n = 30)	PANSS-EC, CGI, and time to sedation: Both treatment groups improve but no differences between them were found.

(continued)

Table 7. Continued

Study	Design	Population	Interventions	Agitation outcomes
Breier et al. (2002)	RCT, double-blind, placebo-controlled. 24 h.	<i>N</i> = 270. Agitation in schizophrenia, schizophreniform or schizoaffective disorder	(2) Haloperidol i.m. <i>plus</i> lorazepam i.m. ( <i>n</i> = 30) (1) Olanzapine i.m. 2.5 mg ( <i>n</i> = 48) (2) Olanzapine i.m. 5 mg ( <i>n</i> = 45) (3) Olanzapine i.m. 7.5 mg ( <i>n</i> = 46) (4) Olanzapine i.m. 10 mg ( <i>n</i> = 46) (5) Haloperidol i.m. 7.5 mg ( <i>n</i> = 40) (6) Placebo i.m. ( <i>n</i> = 45)	PANSS-EC at 2 h: All olanzapine groups were associated with significant decreases compared with placebo (all, $P \leq 0.01$ ). Haloperidol group also presented significant decreases compared with placebo from 60 min to 2 h (all, $P < 0.001$ ).
Taymeeyapradit and Kuasirikul (2002)	RCT, double-blind. 7 days.	<i>N</i> = 70. Agitation and aggression in psychotic patients (schizophrenia and mania).	(1) Zuclopenthixol acetate i.m. 50–100 mg ( <i>n</i> = 38) (2) Haloperidol i.m. 5–10 mg ( <i>n</i> = 32)	BPRS and CGI at 7 days: Both treatment groups improve but no differences between them were found. The zuclopenthixol group required less i.m. administrations than haloperidol ( $P < 0.05$ ).
TREC (2003)	Randomised, pragmatic, single-blind, multisite. 2 weeks.	<i>N</i> = 301. Agitation in with unspecified psychosis or substance use. Psychiatric emergency service.	(1) Haloperidol i.m. 5–10 mg <i>plus</i> promethazine i.m. 50 mg ( <i>n</i> = 150) (2) Midazolam i.m. ( <i>n</i> = 151)	Tranquillisation or asleep by 20 min: The combination group and the midazolam group did not presented differences.
Alexander (2004)	Randomised, pragmatic. 2 weeks.	<i>N</i> = 200. Psychiatric emergency services.	(1) Haloperidol i.m. 10 mg <i>plus</i> promethazine i.m. 25–50 mg ( <i>n</i> = 100) (2) Lorazepam i.m. 4 mg ( <i>n</i> = 100)	Tranquil or asleep: The combination group treatment resulted in more people being tranquil/asleep by 15 min, 30 min, 1 h and 2 h ( $P < 0.05$ ). Onset of tranquillisation/sedation: The combination group treatment resulted in a faster onset.
Nobay et al. (2004)	RCT, double-blind. 24 h.	<i>N</i> = 111. Agitation in unspecified psychosis or substance use. Emergency department.	(1) Midazolam i.m. 5 mg ( <i>n</i> = 42) (2) Lorazepam i.m. 2 mg ( <i>n</i> = 27) (3) Haloperidol i.m. 5 mg ( <i>n</i> = 42)	Modified Thomas Combativeness Scale: Midazolam onset of action was the shorter compared with the lorazepam and haloperidol group ( $P = 0.039$ , midazolam vs. haloperidol; $P = 0.003$ , midazolam vs. lorazepam).
Currier et al. (2004)	RCT, single-blind, prospective, multisite, non-inferiority. 24 h.	<i>N</i> = 162. Psychotic agitation in schizophrenia or schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorders.	(1) Risperidone i.m. 2 mg/day ( <i>n</i> = 83) (2) Haloperidol i.m. 5 mg/day ( <i>n</i> = 79)	PANSS-EC at 30, 60, 120 min: Both agents significantly improved ( $P < 0.001$ ), with no significant difference between groups.
Martel et al. (2005)	RCT, double-blind.	<i>N</i> = 144. Undifferentiated agitation. Emergency department.	(1) Droperidol i.m. 5 mg ( <i>n</i> = 50) (2) Ziprasidone i.m. 20 mg ( <i>n</i> = 46) (3) Midazolam i.m. 5 mg ( <i>n</i> = 48)	Sedation according to the AMS: Adequate sedation achieved at 15 min in patients receiving midazolam, and 30 min for patients receiving droperidol and ziprasidone.
Brook et al. (2005)	Randomised, OL, multisite. Two phase: 3 days + 6 week.	<i>N</i> = 567. Agitation in acute exacerbations of schizophrenia or schizoaffective disorder. Inpatients.	(1) Ziprasidone i.m. 10 or 20 mg; maximum 40 mg/day ( <i>n</i> = 429) (2) Haloperidol i.m. 2.5–5 mg; maximum 10 mg/day ( <i>n</i> = 138)	BPRS at 3 days: Significantly improved in the ziprasidone group compared with haloperidol ( $P < 0.002$ ).
Preval et al. (2005)	Observational.	<i>N</i> = 119. Agitation in psychoses or alcohol/drug intoxication. Psychiatric emergency department.	(1) Ziprasidone i.m. 20 mg ( <i>n</i> = 110) (2) Conventional i.m. antipsychotics ( <i>n</i> = 9)	BARS at 2 h: Both treatment groups improved with no differences between them ( $P < 0.05$ ).
Andrezina et al. (2006a)	RCT, double-blind, placebo controlled, multisite. 24 h.	<i>N</i> = 448. Agitation in schizophrenia and schizoaffective disorder. Inpatients.	(1) Aripiprazole i.m. 9.75 mg ( <i>n</i> = 175) (2) Haloperidol i.m. 6.5 mg ( <i>n</i> = 185) (3) Placebo i.m. ( <i>n</i> = 88)	PANSS-EC at 2 h: The mean improvement was significantly greater in both aripiprazole and haloperidol groups than with placebo i.m. ( $P < 0.001$ ).

(continued)

Table 7. Continued

Study	Design	Population	Interventions	Agitation outcomes
Veser et al. (2006)	RCT, double-blind, placebo-controlled. 90 min.	N = 30. Agitated patients with psychosis. Medical emergency department.	(1) Risperidone p.o. 2 mg/day plus lorazepam i.m. 2 mg/day (n = 10) (2) Haloperidol i.m. 5 mg/day plus lorazepam i.m. 2 mg/(n = 10) (3) Placebo i.m. plus lorazepam i.m. 2 mg/day (n = 10)	PANSS total scores at 30 and 90 min: No significant differences between treatment groups.
Zimbardo et al. (2007)	RCT, double-blind, placebo controlled, multisite. 24 h.	N = 301. Agitation in bipolar disorder (manic and mixed episodes). Inpatients.	(1) Aripiprazole 9.75 mg (n = 75) (2) Aripiprazole 15 mg (n = 75) (3) Lorazepam 2 mg (n = 68) (4) Placebo (n = 73)	PANSS-EC at 2 h: Both aripiprazole treatment groups produced significant improvement compared with placebo (P < 0.001).
Tran-Johnson et al. (2007)	RCT, double-blind, placebo controlled, multisite. 24 h.	N = 357. Agitation in schizophrenia and schizophreniform disorder. Inpatients.	(1) Aripiprazole i.m. 1 mg (2) Aripiprazole i.m. 5.25 mg (3) Aripiprazole i.m. 9.75 mg (4) Aripiprazole i.m. 15 mg (5) Placebo i.m.	PANSS-EC at 2 h: All aripiprazole treatment groups presented significant great improvement compared with placebo.
Daniel et al. (2007)	RCT, two-phase, double-blind. Multisite. 24 h.	N = 448. Agitation in schizophrenia (73%) or schizoaffective disorder (27%). Inpatients.	(1) Aripiprazole i.m. 9.75 mg (n = 175) (2) Haloperidol i.m. 5 mg (n = 185) (3) Placebo i.m. (n = 88)	PANSS-EC at 2 h: Aripiprazole and haloperidol i.m. groups both showed significant improvements (P < 0.001) compared to placebo.
Raveendran et al. (2007)	Randomised, single-blind. 2 weeks.	N = 300. Agitation in unspecified psychiatric illness. Psychiatric emergency service.	(1) Haloperidol i.m. 10 mg plus promethazine i.m. 25 to 50 mg (n = 150) (2) Olanzapine i.m. 10 mg (n = 150)	Tranquil or asleep at 15 and 240 min: Both treatment groups improved but with no differences between them.
Huf et al. (2007)	Pragmatic, randomised, controlled.	N = 316. Agitation in unspecified psychosis or substance use.	(1) Haloperidol i.m. 5–10 mg (2) Haloperidol i.m. 5–10 mg plus promethazine i.m. 50 mg	Tranquillisation or asleep by 20 min: The combination group was more likely to be tranquil or asleep within 20 min than those who received i.m. haloperidol alone.
Agid et al. (2008)	RCT, double-blind. 24 h.	N = 79. Acute agitation in schizophrenia (54%), schizoaffective disorder (27%), bipolar disorder with psychotic features (15%), and psychotic disorder not otherwise specified (4%).	(1) Ziprasidone i.m. 2–8 mg (n = 38) (2) Ziprasidone i.m. 20–80 mg (n = 41)	PANSS-EC at 4 and 24 h: Ziprasidone 20 mg group produced significant great reduction than 2-mg group at 4 (P = 0.02). There was no difference between groups at 24 h.
Wilhelm et al. (2008)	Observational, OL, prospective, multisite. 5 days.	N = 558. Agitation in psychiatric patients: schizophrenia (n = 330), substance use disorder (n = 98), mood disorders (n = 88) and others (n = 42). Psychiatric emergency setting or inpatient.	(1) Haloperidol i.m. (n = 132) (2) Olanzapine i.m. (n = 389) (3) Risperidone i.m. (n = 72)	PANSS-EC, CGI-A at 2 days: Improvement in all treatment groups with no differences between groups. Sedation score at 2 days: Olanzapine group was less sedated than others according to a tranquillisation score
Chandrasena et al. (2009)	Observational, multisite. 7 days.	N = 2011. Agitation in schizophrenia (70%) and bipolar disorder (acute mania). Emergency psychiatric settings and inpatients.	(1) Olanzapine i.m. (n = 1294) (2) Other i.m. antipsychotic (n = 717)	Safety and tolerability: The olanzapine group experienced less adverse event than patients in the other i.m. antipsychotic group (34.4 vs. 46.2%, P < 0.001).
Castle et al. (2009)	Observational. Multisite. 7 days.	N = 2011. Agitation in schizophrenia (70%) and bipolar disorder (acute mania). Emergency psychiatric settings and inpatients.	(1) Olanzapine i.m. (n = 1294) (2) Other i.m. antipsychotic (n = 717)	PANSS-EC and CGI-S at 2 h: Significantly greater in i.m. olanzapine group compared with other i.m. antipsychotics (P < 0.05).
Hsu et al. (2010)	RCT, single-blind, prospective, multisite. 24 h.	N = 42. Agitation in psychosis (schizophrenia, bipolar I disorder, schizoaffective disorder, delusional disorder, or other psychotic disorders). Inpatients.	(1) Olanzapine i.m. 10 mg (n = 11) (2) Haloperidol i.m. 7.5 mg (n = 11) (3) Olanzapine ODT 10 mg (n = 10) (4) Risperidone OS 3 mg (n = 10)	PANSS-EC: Both olanzapine treatment groups presented significant decreases before 90 min post-treatment compared with the haloperidol group.

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Table 7. Continued

Study	Design	Population	Interventions	Agitation outcomes
Isbister et al. (2010)	RCT, single-blind. 6 h.	N = 91. Emergency department.	(1) Droperidol i.m. 10 mg (n = 33) (2) Midazolam i.m. 5 mg (n = 29) (3) Droperidol i.m. 10 mg plus Midazolam i.m. 5 mg (n = 29)	Duration of agitation: No differences between the different treatment groups.
MacDonald et al. (2010)	Observational.	N = 105. Agitation in alcohol/drug intoxicated patients.	(1) Haloperidol i.m. ± lorazepam i.m. as needed (2) Olanzapine i.m. ± lorazepam i.m. as needed	Additional medication intervention at 3 h: Haloperidol plus benzodiazepine and olanzapine performed better results than haloperidol alone.
Baldaçara et al. (2011)	RCT, double-blind. 12 h.	N = 150. Agitation in psychosis (60.6%) and bipolar disorder (39.4%). Psychiatric emergency service.	(1) Olanzapine i.m. 10 mg (n = 30) (2) Ziprasidone i.m. 20 mg (n = 30) (3) Haloperidol i.m. 5 mg plus promethazine i.m. 50 mg (n = 30) (4) Haloperidol i.m. 5 mg plus midazolam i.m. 15 mg (n = 30)	OAS, OAS at 12 h: All treatment groups improved significantly the OAS and OAS with worst results in the haloperidol plus midazolam group (P < 0.001).
Mautone et al. (2011)	OL, non-controlled, multisite. Two phase: 3 days + 8 weeks.	N = 150. Agitation in schizophrenia. Inpatient.	(5) Haloperidol i.m. 5 mg (n = 30) (1) Ziprasidone i.m. 10–40 mg (2) Ziprasidone p.o. 80–160 mg	PANSS and CGI-5 at 3 days and 8 weeks: Significantly decreases in the i.m. and oral ziprasidone treatment phases (P < 0.0001) BARS at 4 h: BARS response approximately 3 h after first injection of ziprasidone. Length of stay: No statistically significant difference between treatment groups (P = 0.75).
Leung et al. (2011)	Observational.	N = 136. Agitation in schizophrenia or schizoaffective disorder. Inpatient.	(1) Haloperidol i.m. 5–10 mg (n = 49) (2) SGA i.m.: ziprasidone 10–20 mg (n = 47), olanzapine 5–20 mg (n = 33), aripiprazole 9.75 mg (n = 7).	
Perrin et al. (2012)	Observational. Multisite. 24 h.	N = 1945. Agitation in schizophrenia and bipolar mania.	(1) Olanzapine i.m. (n = 696) (2) Other i.m. psychotropic medications (n = 1244)	PANSS-EC at 1 and 24 h: Improvement in both treatment groups with no differences between groups.
MacDonald et al. (2012)	Observational. Multisite. 3 h.	N = 146. Agitated medical (n = 66) and psychiatric patients (n = 80). Emergency department and psychiatric emergency service.	(1) Haloperidol i.m. 5 mg (n = 42) (2) Haloperidol i.m. 5 mg plus lorazepam i.m. 2 mg (n = 72) (3) Olanzapine i.m. 10 mg (n = 21) (4) Olanzapine i.m. 10 mg plus lorazepam i.m. 2 mg (n = 11)	Percentage of additional medication intervention at 3 h: Olanzapine alone (29%) or in combination with lorazepam (9%), was substantially lower than haloperidol monotherapy (43%) and similar to the haloperidol plus lorazepam (18%).
Mantovani et al. (2013)	RCT, single-blind. 24 h.	N = 100. Agitation in psychiatric patients. Emergency psychiatric service.	(1) Haloperidol i.m. 2.5 mg plus promethazine i.m. 25 mg (HLP plus PMZ; n = 27) (2) Haloperidol i.m. 2.5 mg plus midazolam i.m. 7.5 mg (HLP plus MID; n = 25) (3) Ziprasidone i.m. 10 mg (n = 23) (4) Olanzapine i.m. 10 mg (n = 25)	ACES and PANSS-EC scores at 30, 60, 90 min: All treatment groups showed a reduction in agitation (P < 0.001), with significant lower reduction in HLP plus PMZ (P = 0.038) and ziprasidone (P = 0.043) compared with HLP plus MID and olanzapine.
Katagiri et al. (2013)	RCT, double-blind, placebo controlled, parallel-group, multisite. 24 h.	N = 90. Agitation in schizophrenia. Inpatients.	(1) Olanzapine i.m. 10 mg (n = 45) (2) Placebo i.m. (n = 45)	PANSS-EC at 2 h: Olanzapine group showed a significant decrease compared with the placebo group (P < 0.001).
Zhang et al. (2013)	RCT, single-blind, active-controlled, parallel-group, multisite. 72 h.	N = 376. Agitation in schizophrenia.	(1) Ziprasidone i.m. 10–40 mg (n = 189) (2) Haloperidol i.m. 5–20 mg (n = 187)	BARS at 24 and 72 h: No differences between treatment groups.

(continued)

Table 7. Continued

Study	Design	Population	Interventions	Agitation outcomes
De Filippis et al. (2013)	OL, 24 h.	N = 201. Agitation in schizophrenia and bipolar disorder. Acute psychiatric care wards.	(1) Aripiprazole i.m. 9.75 mg	PANSS-EC, ACES and CGI-I at 30, 60, 90, 120 min and 24 h: Aripiprazole significantly improved all clinical measures.
Chan et al. (2014)	RCT, double-blind, parallel group, multisite; 2 h.	N = 49. Agitation in schizophrenia. Inpatients.	(1) Olanzapine i.m. 10 mg (n = 25) (2) Haloperidol i.m. 7.5 mg (n = 24)	PANSS-EC at 2 h: Improvement in both treatment groups with no differences between groups.
Suzuki et al. (2014)	Observational 1 h.	N = 122. Agitation in schizophrenia. Inpatients.	(1) Olanzapine i.m. 5–10 mg (n = 44) (2) Haloperidol i.m. 2.5–5 mg (n = 41) (3) Levomepromazine i.m. 25 mg (n = 37)	PANSS-EC and ACES at 1 h: Both olanzapine and levomepromazine groups presented significant improvement compared with the haloperidol group.

OL, Open Label; RCT, Randomised Controlled Trial; p.o., oral; i.m., intramuscular; ODT, oro-dispersible tablets; OS, oral solution; ABS, Agitated Behaviour Scale; ACES, Agitation and Calmness Evaluation Scale; AMS, Altered Mental Status; BARS, Behavioural Activity Rating scale; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; MOAS, Modified Overt Aggression Scale; OAS, Overt Aggression Scale; OASS, Overt Agitation Severity Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale – Excited Component; HLP, haloperidol; PMZ, promethazine; SGA, Second Generation Antipsychotic.

in 301 agitated patients with unspecified psychosis or substance use. Both treatments were effective, but midazolam was clearly more effective than the combination in terms of rapid sedation at 20 min (32% more patients sedated in the midazolam group, *P* not reported) (Huf et al. 2002; TREC 2003). Severe AEs were rare. In a 2-week, randomised trial comparing an i.m. combination of haloperidol (10 mg) and promethazine (25–50 mg) vs. i.m. lorazepam (4 mg) in 200 agitated psychiatric patients in a psychiatric emergency service Alexander (2004) found a similar percentage of “sedated or asleep” patients at 4 h in both groups (96%). The combination treatment resulted in more patients being sedated at 15 min, 30 min, 1 h and 2 h, with also a faster onset of tranquillization and a greater clinical improvement over the first 2 h. In this trial, neither intervention differed significantly in the AEs profile. Another trial that compared i.m. BZDs with FGA was a 1-day, randomised, double-blind trial that evaluated i.m. midazolam (5 mg), i.m. haloperidol (5 mg) and i.m. lorazepam (2 mg) in 111 violent or agitated patients with unspecified psychosis or substance use (Nobay et al. 2004). The authors found that midazolam has a faster onset of action compared with the other treatment groups according to the Modified Thomas Combativeness Scale (mean of 18.3 min to sedation for midazolam, 28.3 min for haloperidol and 32.2 min for lorazepam; *P* = 0.039, midazolam vs. haloperidol; *P* = 0.003, midazolam vs. lorazepam). In addition, there were no significant differences in the AEs profile. I.m. midazolam *plus* i.m. haloperidol was as effective as i.m. olanzapine and better than haloperidol *plus* promethazine and i.m. ziprasidone in the management of psychiatric agitation according to the PANSS-EC (Mantovani et al. 2013).

Intramuscular midazolam has been compared to i.m. droperidol in two randomised controlled trials. In the first (Martel et al. 2005), i.m. midazolam (5 mg) was as effective as droperidol (5 mg) and ziprasidone (20 mg) according to the Altered Mental Status (AMS) at 2 h. Despite the equal results, authors noticed that patients receiving midazolam more frequently required additional sedation (*P* < 0.05). No major AEs differences between treatments were found. The second randomised trial that tested the efficacy of i.m. midazolam (10 mg) with droperidol (10 mg) in 91 patients in the emergency department (Isbister et al. 2010) did not find differences in effectiveness. Additionally, as it was mentioned with the previous trial, the authors also pointed out that the i.m. midazolam group required additional sedation to achieve the anti-agitation effect and presented more AEs (over-sedation).

The efficacy of i.m. BZDs was also compared with olanzapine in a 24-h, randomised, double-blind trial.

Meehan and colleagues (2001) evaluated the efficacy of i.m. olanzapine (10 mg), i.m. lorazepam (2 mg), and placebo in 201 agitated patients with bipolar I disorder. At 2 h after the first injection, patients treated with i.m. olanzapine showed a significantly greater reduction in PANSS-EC scores compared with those treated with either placebo or lorazepam. No significant differences among the three treatment arms were observed regarding the AEs profile.

Regarding the efficacy of i.m. BZDs vs. i.m. aripiprazole, a 24-h, multisite, randomised, double-blind, placebo controlled trial in 301 acutely agitated inpatients with bipolar I diagnoses (manic or mixed episode) compared the efficacy of i.m. aripiprazole in two different dosages (9.75 mg,  $n = 78$ ; and 15 mg,  $n = 78$ ), i.m. lorazepam (2 mg;  $n = 70$ ), or placebo ( $n = 75$ ) (Zimbroff et al. 2007). All active treatment groups significantly improved PANSS-EC scores at 2 h post injection compared with placebo ( $P < 0.001$ ). Authors also noticed that both aripiprazole doses were well tolerated and sedation was less frequent with aripiprazole 9.75 mg than with aripiprazole 15 mg or lorazepam 2 mg, suggesting a better risk–benefit AE profile for i.m. aripiprazole 9.75 mg compared to aripiprazole 15 mg or lorazepam 2 mg.

As mentioned above, the literature search reported three trials where oral risperidone *plus* i.m. lorazepam was compared to i.m. haloperidol *plus* i.m. lorazepam. In none of these three randomised trials, the adjunctive treatment with i.m. lorazepam added any significant beneficial anti-agitation effect in terms of PANSS-EC (Currier and Simpson 2001; Currier et al. 2004; Veser et al. 2006), although in one trial, all combination treatment options (oral risperidone *plus* i.m. lorazepam and i.m. haloperidol *plus* i.m. lorazepam) were superior to lorazepam in monotherapy (Veser et al. 2006).

**First generation antipsychotics (FGAs).** First generation antipsychotics have been the mainstay of agitation treatment, with haloperidol being the most studied and used drug in the management of acute agitation. Furthermore, haloperidol has become the gold standard comparator for most trials in the field of psychomotor agitation (Fitzgerald 1969; Fruensgaard et al. 1977; Paprocki 1977; Stotsky 1977; Tuason 1986; Schleifer 2011).

To our knowledge, the first trial performed with FGAs is a 3-day, randomised double-blind trial of 30 agitated psychotic patients (Man and Chen 1973). Subjects allocated to the i.m. chlorpromazine (50 mg) group did not differ in the agitation outcomes (number of additional injections needed to treat agitation) compared to those allocated to i.m. haloperidol (5 mg)

group. Another early randomised, double-blind trial (Resnick and Burton 1984) compared a single dose of i.m. droperidol (5 mg) and i.m. haloperidol (5 mg) in 27 patients with agitation and unspecified psychosis. According to the BPRS mean total scores, there was a significantly greater reduction in agitation at 30 min in the droperidol treatment group compared to haloperidol ( $P < 0.05$ ).

Intramuscular haloperidol (5–10 mg) in monotherapy has been compared to the combination of i.m. haloperidol (5–10 mg) *plus* promethazine (50 mg) in a randomised, open-label study performed in 316 agitated patients with unspecified psychosis or substance use. Patients in the combination group were more likely to be tranquil or asleep within 20 min than those who received haloperidol alone ( $P = 0.002$ ), needed fewer additional medications and presented less frequently with acute dystonia (Huf et al. 2007). In another randomised controlled trial, the efficacy of i.m. droperidol (10 mg) was compared with i.m. midazolam (10 mg) and with their combination in 91 patients that required physical restraint in the emergency department (Isbister et al. 2010). In this study, no differences were found amongst the three groups regarding the median duration of the agitated behaviour (20 min for droperidol, 24 min for midazolam, and 25 min for the combination). Furthermore, i.m. midazolam treatment needed more additional sedative medications and presented with a higher rate of AE (over-sedation) compared to droperidol.

Zuclopenthixol acetate has been traditionally considered a treatment of choice when longer-term sedation is required. In a 7-day, randomised, double-blind study (Taymeeyapradit and Kuasirikul 2002) that compared i.m. zuclopenthixol acetate (50–100 mg;  $n = 38$ ) with i.m. haloperidol (5–10 mg;  $n = 32$ ) for the treatment of acute psychotic patients with aggression there was no statistically significant difference in reduction of aggression based on BPRS rating and CGI scores between the two groups, but patients allocated in the zuclopenthixol group required less i.m. administrations than those on the haloperidol ( $P < 0.05$ ).

**First generation antipsychotics (FGAs) versus benzodiazepines (BZDs).** As it was mentioned previously in the i.m. BZDs section, the literature search retrieved eight studies of haloperidol (alone or in combination with BZDs or promethazine) and two studies of droperidol where these agents were compared to BZDs.

In three of them, with a similar study design (randomised, double-blind), i.m. haloperidol alone came out as equally effective as i.m. lorazepam (Lenox et al. 1992; Battaglia et al. 1997; Nobay et al. 2004).

However, when i.m. haloperidol *plus* i.m. lorazepam (Battaglia et al. 1997; Bieniek et al. 1998) or i.m. haloperidol *plus* i.m. promethazine were compared to i.m. lorazepam alone (Alexander 2004), the combination treatment groups were superior in terms of agitation outcomes.

When haloperidol was compared with other BZDs, i.m. haloperidol was equally effective as i.m. clonazepam (Chouinard et al. 1993), i.m. flunitrazepam (Dorevitch et al. 1999) and i.m. midazolam (Nobay et al. 2004) in the management of agitation. Nevertheless, i.m. midazolam compared to i.m. haloperidol *plus* promethazine was significantly superior to the combination treatment (Huf et al. 2002; TREC 2003) but equally effective to i.m. droperidol (Martel et al. 2005; Isbister et al. 2010) and the combination of i.m. droperidol *plus* midazolam (Isbister et al. 2010).

*First generation antipsychotics (FGAs) versus second generation antipsychotics (SGAs).* Some other studies have compared the effectiveness of i.m. haloperidol (alone or in combination) vs. other i.m. SGAs.

Wright et al. (2001) were the first to compare i.m. olanzapine (10 mg) with i.m. haloperidol (5 mg) and placebo in 311 acutely agitated psychotic patients. As results, haloperidol was equally effective than olanzapine but superior to placebo in the management of psychotic agitation according to the PANSS-EC.

Martel et al. (2005) studied the efficacy of i.m. droperidol (5 mg), ziprasidone (20 mg), and midazolam (5 mg) in a randomised, double-blind trial in 144 agitated patients visiting an emergency department. All three drugs were equally effective in managing acute agitation according to the Altered Mental Status (AMS) at 2 h (all,  $p < 0.05$ ), although with ziprasidone more patients remained agitated at 15 min compared with the other agents evaluated, and patients receiving midazolam more frequently required additional sedation ( $P < 0.05$ ). No differences in major AEs between treatments were found.

A 2-week, randomised, single-blinded trial compared i.m. haloperidol (10 mg) *plus* promethazine (25–50 mg) with i.m. olanzapine (10 mg) in 300 agitated patients with unspecified mental illness in a psychiatric emergency setting (Raveendran et al. 2007). No statistical differences were found amongst the two groups regarding the primary outcomes measures (proportions of people being tranquil or asleep at 15 and 240 min;  $P = 0.2$ ). However, haloperidol *plus* promethazine sedated patients more rapidly, with 14% more patients being asleep at 15 min. In addition, more patients given olanzapine than those given the combination treatment

required additional drugs over 4 h. In addition, serious AEs were not seen with either intervention.

In an observational study in 105 agitated patients visiting an emergency department who received either i.m. haloperidol or i.m. olanzapine (*plus* lorazepam as needed), the authors found that in alcohol/drug-intoxicated patients, the haloperidol *plus* BZD treatment group and the olanzapine group performed better than haloperidol alone with no evidence of severe AEs in any group (MacDonald et al. 2010). More recently, the same authors performed another observational study in 146 agitated patients who received either i.m. haloperidol (5 mg) or i.m. olanzapine (10 mg) (with or without BZDs) in an emergency department. The percentage of additional medications required in the olanzapine group was substantially lower than in the haloperidol monotherapy group (43%) and similar to the haloperidol *plus* BZD group (18%). The results of this study suggest that haloperidol in monotherapy is less effective in managing agitation (at least in requiring additional medication) than olanzapine with or without a BZD or haloperidol *plus* a BZD (MacDonald et al. 2012).

A 5-day, multisite, observational, open-label study in 558 acutely psychiatric agitated patients (IMPULSE) evaluated the short-term effectiveness and tolerability of SGAs compared to FGAs (Wilhelm et al. 2008). In this study, treatment options were: haloperidol ( $n = 132$ ), olanzapine ( $n = 389$ ) and risperidone ( $n = 72$ ). The PANSS-EC and the CGI-aggression scores improved in all treatment group comparisons (olanzapine vs. non-olanzapine, risperidone vs. non-risperidone, haloperidol vs. non-haloperidol;  $P > 0.05$  for all comparisons). However, the authors found that concomitant BZD use was more frequent in patients receiving haloperidol (haloperidol vs. non-haloperidol:  $P < 0.001$ ). Later, when i.m. haloperidol was compared with risperidone oral solution (OS) and olanzapine (both ODT and i.m.), it was found that i.m. haloperidol had a similar efficacy compared to risperidone OS but was less effective compared to both olanzapine formulations (Hsu et al. 2010) regarding the PANSS-EC scores at 90 min.

Leung et al. (2011) performed an observational study to evaluate the length of stay (LOS) in the hospital from the time of first injection until discharge in agitated patients treated with i.m. haloperidol compared to i.m. SGAs. One hundred and thirty-six inpatients with schizophrenia or schizoaffective disorder were assigned to four treatment groups: i.m. haloperidol (5–10 mg;  $n = 49$ ), i.m. ziprasidone (10–20 mg;  $n = 47$ ), i.m. olanzapine (5–20 mg;  $n = 33$ ), i.m. aripiprazole (9.75 mg;  $n = 7$ ). There were no statistical significant differences in the LOS ( $P = 0.75$ ) when comparing the haloperidol group

with the overall SGAs group. However, there were statistically significant differences in terms of both costs and number of injections required amongst the 4 groups, favouring the haloperidol group. Additionally, amongst the SGA used in the study, ziprasidone was associated with a shorter LOS compared to olanzapine ( $P=0.026$ ).

Another randomised trial compared the effectiveness of i.m. olanzapine (10 mg;  $n=30$ ), i.m. ziprasidone (20 mg;  $n=30$ ), i.m. haloperidol plus promethazine (5 plus 50 mg;  $n=30$ ), i.m. haloperidol plus midazolam (5 plus 15 mg;  $n=30$ ) and i.m. haloperidol alone (5 mg;  $n=30$ ) in 150 agitated patients with psychosis or bipolar disorder (manic or mixed episode) (Baldaçara et al. 2011). Both the OASS and the OAS improved significantly in all treatment groups at the endpoint (12 h); however, patients treated with haloperidol plus midazolam had still high levels of agitation and aggression ( $P<0.001$ ), more AEs ( $P<0.001$ ), and required physical restraint (70%) compared to the other treatment groups (Baldaçara et al. 2011).

In a randomised, rater-blinded study in 100 acutely agitated psychiatric patients with different diagnoses, Mantovani et al. (2013) compared the efficacy and safety of i.m. haloperidol plus promethazine (2.5 plus 25 mg;  $n=27$ ), i.m. haloperidol plus midazolam (2.5 plus 7.5 mg;  $n=25$ ), i.m. ziprasidone (10 mg;  $n=23$ ), or i.m. olanzapine (10 mg;  $n=25$ ). Overall, all treatment options showed a reduction in agitation, without causing excessive sedation ( $P<0.001$ ) according to the PANSS-EC, although less reduction in agitation was observed with the combination haloperidol plus promethazine ( $P=0.038$ ) and ziprasidone ( $P=0.043$ ) compared to haloperidol plus midazolam and olanzapine. In conclusion, the authors noticed that low doses of haloperidol combined with midazolam are as effective as olanzapine in reducing psychomotor agitation but better tolerated than haloperidol plus promethazine in terms of EPS (Mantovani et al. 2013).

The most recent study that compared i.m. haloperidol to i.m. olanzapine and i.m. levomepromazine found a significant improvement in the PANSS-EC in favour of the olanzapine and levomepromazine group (Suzuki et al. 2014) in a sample of psychotic agitated patients. In contrast, Chan et al. (2014) found i.m. haloperidol as effective as i.m. olanzapine in terms of improvement in the PANSS-EC scores at 2 h in a sample of acute agitated schizophrenic patients.

When i.m. haloperidol was compared to i.m. aripiprazole in the management of acute agitation in patients with schizophrenia, of the three randomised controlled trials two found aripiprazole more effective than haloperidol (Andrezina et al. 2006a; Tran-Johnson et al. 2007)

and one aripiprazole as effective as haloperidol (Daniel et al. 2007) according to the PANSS-EC.

When compared to i.m. ziprasidone, i.m. haloperidol has been also reported as equally effective or non-superior according to the BPRS agitation sub-scale score (Brook et al. 2000, 2005; Zhang et al. 2013) and the BARS (Preval et al. 2005) in acutely psychotic patients and alcohol/drug intoxication (Preval et al. 2005). However, i.m. ziprasidone had lower rates of EPS and less need for additional medication than the haloperidol group (Brook et al. 2000, 2005; Preval et al. 2005; Zhang et al. 2013).

### *Second generation antipsychotics (SGAs).*

*Olanzapine.* The most robust scientific evidence exists for i.m. olanzapine in agitated psychiatric patients. The first trial that compared i.m. olanzapine (10 mg) with i.m. haloperidol (5 mg) and placebo was a 24-h, randomised, double-blind, placebo controlled trial in 311 patients with acute agitation and schizophrenia, schizophreniform or schizoaffective disorder (Wright et al. 2001). In this study, treatment with olanzapine was associated with significant decreases in PANSS-EC scores from 15 to 45 min compared to haloperidol ( $P<0.01$ ) and from 15 min to 2 h compared to placebo (all,  $P<0.05$ ). Olanzapine was superior to placebo and non-inferior to haloperidol in the management of psychotic agitation. The authors also pointed out that motor AEs (EPS) were more frequent in the haloperidol group ( $P<0.001$ ) than in the olanzapine or placebo group. No differences were found regarding other AEs. When compared to BZDs (i.m. lorazepam 2 mg), i.m. olanzapine (10 mg) showed greater improvement according to the PANSS-EC at 2 h (Meehan et al. 2001). In another 24-h, randomised, double-blind, placebo controlled trial, Breier et al. (2002) compared the efficacy of i.m. olanzapine (2.5 to 10 mg) with i.m. haloperidol (7.5 mg) and placebo in 270 agitated psychotic patients (schizophrenia, schizophreniform or schizoaffective disorder). Both olanzapine doses and haloperidol were associated with significant decreases in PANSS-EC scores at 2 h, compared to placebo (all,  $P\leq 0.01$  and  $P<0.001$ , respectively). Although all olanzapine treatment groups did not show superiority compared to haloperidol, the authors suggested that olanzapine 10 mg may have advantages in terms of efficacy compared to olanzapine 7.5 mg and haloperidol due to the more rapid onset and the persistence of action at 24 h. Overall, the most frequently reported AE was hypotension. Neither the rate of hypotension nor EPS was different between groups. Raveendran et al. (2007) performed a randomised, single-blinded trial where i.m. olanzapine was as effective as haloperidol plus promethazine with regards

to the proportions of people being tranquil or asleep at 4 h, although the combination treatment had a more rapid onset of action and required less additional medication in comparison to i.m. olanzapine (Raveendran et al. 2007).

In a randomised trial that compared both olanzapine ODT and i.m. olanzapine with i.m. haloperidol and risperidone OS, i.m. olanzapine was as effective as the oral formulation according to the PANSS-EC at 90 min. Nevertheless, both olanzapine formulations were more effective than i.m. haloperidol. Drowsiness was the most common AE, with no differences between treatments (Hsu et al. 2010).

In two observational studies of agitated patients who received either i.m. olanzapine or i.m. haloperidol (*plus* lorazepam as needed), i.m. olanzapine was more effective than i.m. haloperidol in alcohol/drug intoxicated patients (MacDonald et al. 2010) and with regards to additional medication required (MacDonald et al. 2012). Recently, Chan et al. (2014) compared the efficacy and safety of i.m. olanzapine (10 mg;  $n = 25$ ) vs. i.m. haloperidol (7.5 mg;  $n = 24$ ) in agitated hospitalised patients with schizophrenia in a 2-h, multisite, randomised, double-blind, parallel study. Both the olanzapine and haloperidol groups showed significant improvement compared to baseline at 2 h in the PANSS-EC score ( $P < 0.001$ ), with no significant differences between the two drugs ( $P = 0.254$ ). Furthermore, insomnia was the most common AE, no serious AEs were reported, and no significant differences between treatment groups were found regarding other AE.

The effectiveness and tolerability of i.m. olanzapine ( $n = 1294$ ) vs. short-acting i.m. FGAs (haloperidol and zuclopenthixol;  $n = 717$ ) for the treatment of agitated patients with schizophrenia or acute mania has been assessed in a large ( $n = 2011$ ), multisite, observational study (Castle et al. 2009). The authors found that olanzapine was slightly more effective than the other antipsychotics (measured by the PANSS-EC score at 2 h;  $P < 0.05$ ). A second report from the same large sample (Chandrasena et al. 2009) compared the safety and tolerability of i.m. olanzapine vs. these i.m. FGAs in the treatment of acute agitation. This secondary analysis found that patients treated with olanzapine experienced significantly fewer EPS ( $P < 0.001$ ) and used significantly less oral concomitant medication ( $P = 0.009$ ) than patients who received the other i.m. antipsychotics.

Perrin et al. (2012) performed a 24-h, multisite, observational study to assess early effectiveness and tolerability of i.m. psychotropic treatment in a large sample of 1945 acutely agitated patients with schizophrenia or bipolar mania. Overall, olanzapine was the most commonly administered initial medication

( $n = 696$ ), followed by haloperidol ( $n = 451$ ). Clinical improvement was significantly better in the olanzapine group compared to the non-olanzapine patients at 24 h of treatment ( $P = 0.004$ ) according to the CGI-S mean scores, but no significant differences were found when change was measured with the CGI-I and the PANSS-EC. The most common AEs were somnolence, headache, and asthenia with no differences between treatment groups. However, the rate of EPS was significantly lower in the olanzapine group compared to the non-olanzapine patients ( $P < 0.001$ ). More recently, the efficacy and safety of i.m. olanzapine ( $n = 44$ ; 5, 7.5 or 10 mg) was compared to i.m. haloperidol ( $n = 41$ , 2.5 or 5 mg) and to i.m. levomepromazine ( $n = 37$ ; 25 mg) in 122 acute agitated inpatients with schizophrenia in a 1-h observational naturalistic study design (Suzuki et al. 2014). Both olanzapine and levomepromazine were significantly superior to haloperidol in mean changes from baseline on the PANSS-EC and ACES ( $P < 0.05$ ). Furthermore, compared to haloperidol, olanzapine was also more acting more rapidly and had lower rates of drug-induced EPS. Most AEs were mild or moderate, and no serious AEs were noted. Regarding motor AEs, the presence of EPS was significantly higher with haloperidol and levomepromazine compared to olanzapine ( $P < 0.001$ ).

There is only one paper comparing the efficacy of olanzapine vs. placebo. This recent 24-h, multisite, randomised, placebo-controlled, double-blind, parallel-group trial compared the efficacy of i.m. olanzapine (10 mg) with placebo in 90 agitated schizophrenic inpatients. At 2 h after the injection, the olanzapine group showed a significant decrease in the PANSS-EC total score compared to the placebo group ( $P < 0.001$ ). There were no serious AEs reported, and no significant differences in the proportion of patients experiencing AEs were found between treatment groups (Katagiri et al. 2013).

**Aripiprazole.** Another SGA that has been studied quite well for the management of psychiatric agitation is i.m. aripiprazole. In a 24-h, multisite, randomised, double-blind, placebo controlled trial, i.m. aripiprazole (9.75 mg) was compared to i.m. haloperidol (6.5 mg) and i.m. placebo for the treatment of acute agitation in 448 inpatients with schizophrenia or schizoaffective disorder (Andrezina et al. 2006a). The mean improvement in the PANSS-EC at 2 h was significantly greater in the aripiprazole group vs. placebo ( $P < 0.001$ ), and aripiprazole was also non-inferior to haloperidol. In addition, aripiprazole showed a more rapid onset of action compared to placebo (mean changes in PANSS-EC scores evident after 1 h ( $P < 0.05$ )). Most reported AEs were mild or moderate in severity with no differences

between treatment groups. EPS were similar for aripiprazole (1.7%) and placebo (2.3%) and lower than with haloperidol (12.6%). In a post hoc analysis of this trial focussing on patients with agitation and schizophrenia ( $n=325$ ), aripiprazole was again significantly more effective than placebo in reducing agitation (PANSS-EC mean change at 2 h;  $P<0.01$  vs. placebo) (Andrezina et al. 2006b). Another trial with similar design in acutely agitated psychotic patients ( $n=357$ ) compared the efficacy and safety of i.m. aripiprazole (1, 5.25, 9.75 and 15 mg), i.m. haloperidol (7.5 mg), and placebo (Tran-Johnson et al. 2007). In this trial aripiprazole 9.75 mg had the earliest onset of action (45 min) according to the PANSS-EC scores, compared to all other doses of aripiprazole and haloperidol. Overall, AEs were of mild or moderate severity only, no differences between treatment groups were found, and no evidence for an increased rate of AEs with increasing i.m. aripiprazole dose was found.

Daniel et al. (2007) performed a multisite, randomised, double-blind trial with i.m. aripiprazole (9.75 mg), i.m. haloperidol (6.5 mg) or i.m. placebo in 448 agitated patients with schizophrenia (73%) or schizoaffective disorder (27%) (Daniel et al. 2007). Both aripiprazole and haloperidol groups showed significant improvements on the PANSS-EC mean score at 2 h ( $P<0.001$ ) compared to the placebo group. This study suggests that aripiprazole may be an additional effective option for the management of acute agitation in schizophrenia or schizoaffective disorder. Despite the percentage of AEs was higher in the haloperidol group (44.8%), the difference between treatments was not significant.

When compared to i.m. BZDs, a randomised, double-blind trial found that i.m. lorazepam (2 mg) was as effective as i.m. aripiprazole in relation to the PANSS-EC scores at 2 h, nevertheless aripiprazole 9.75 mg was better tolerated and caused lower levels of sedation compared to aripiprazole 15 mg and lorazepam 2 mg (Zimbroff et al. 2007).

A more recent trial that assessed i.m. aripiprazole (9.75 mg) was a 24-h, multisite, open-label trial of 201 agitated inpatients with schizophrenia or bipolar I disorder. The rate of treatment response was 83.6% after 2 h and, with repeated injections, this rate rose to over 90% after 24 h post-injection. Furthermore, there were no differences in the PANSS-EC changes between the different disorders (schizophrenia vs. bipolar disorder). There was also a lack of relationship between serum levels of aripiprazole and clinical response in these acutely agitated patients, regardless of the underlying psychiatric condition. In addition, no AEs were

reported, probably due to the short observation period (De Filippis et al. 2013).

**Ziprasidone.** The efficacy of i.m. ziprasidone (10–80 mg) was compared to i.m. haloperidol (2.5–20 mg) in a 7-day, multisite, randomised, open-label study in agitated psychotic inpatients (schizophrenia, schizoaffective disorder, bipolar disorder, brief psychotic disorder, or psychotic disorder not otherwise specified) (Brook et al. 2000). Patients assigned to ziprasidone ( $n=90$ ) had a greater improvement in the BPRS total score, in the BPRS agitation items and in the CGI-S total score at endpoint compared to subjects receiving haloperidol ( $n=42$ ) ( $P<0.05$ ,  $P<0.01$  and  $P<0.01$ , respectively). In addition, ziprasidone had lower rates of EPS and less need for additional medication than the haloperidol group. Later, a 6-week, multisite, randomised, open-label trial conducted in 567 agitated inpatients with acute exacerbations of schizophrenia or schizoaffective disorder compared i.m. ziprasidone ( $n=429$ ; 10 or 20 mg) and haloperidol ( $n=138$ ; 2.5–5 mg) (Brook et al. 2005). Overall, ziprasidone treatment resulted in a greater decrease in BPRS scores at the end of the 3-day i.m. treatment period compared to haloperidol ( $P<0.002$ ), but differences between treatment groups were not found in the BPRS scores for anxiety and agitation subscales. Furthermore, haloperidol-treated patients had greater rates of motor AEs (EPS) in comparison to the ziprasidone group ( $P<0.0001$ ). Another study that compared i.m. ziprasidone (20 mg;  $n=110$ ) with i.m. haloperidol or chlorpromazine ( $n=9$ ) in patients with agitation due to alcohol/drug intoxication was performed by Preval et al. (2005). In this naturalistic psychiatric emergency service study, ziprasidone was equally effective in reducing agitation compared to the FGAs and in the BARS score at 15, 30 min and at 2 h ( $P<0.05$  for all determinations). No severe AEs events were reported (Preval et al. 2005). A 72-h, multisite, randomised, single-blind, active-control, parallel-group trial compared the efficacy and tolerability of flexible doses of i.m. ziprasidone (10–40 mg/day;  $n=189$ ) with i.m. haloperidol (5–20 mg/day;  $n=187$ ) in 376 schizophrenic agitated patients (Zhang et al. 2013). In this study, ziprasidone was found to be as effective as haloperidol in the treatment of agitation according to the BPRS agitation subscale score and the BARS score at 2, 4, 24, 48 and 72 h. Moreover, ziprasidone showed a more favourable tolerability and safety profile compared to haloperidol in terms of motor AEs (EPS;  $P=0.001$ ). In another trial that compared i.m. ziprasidone with i.m. olanzapine, i.m. haloperidol plus promethazine and i.m. haloperidol plus midazolam, all treatment options lead to a reduction in agitation (PANSS-EC), but smaller

reductions were observed in the ziprasidone and the haloperidol *plus* promethazine group compared to the other treatment groups (Mantovani et al. 2013).

The efficacy of different i.m. dosages of ziprasidone in subjects with acute psychotic agitation was evaluated in two similarly designed 24-h, multisite, randomised, double-blind trials (Lesem et al. 2001; Daniel et al. 2001). In the first trial, subjects were assigned to receive up to four injections of 2 mg ( $n = 54$ ) or 10 mg ( $n = 63$ ) of i.m. ziprasidone (Lesem et al. 2001). Ziprasidone (10 mg) rapidly reduced symptoms of acute agitation and was significantly more effective ( $P < 0.01$ ) than ziprasidone (2 mg) 4 h after the first injection according to the mean change in the BARS scale score. In the second trial, ziprasidone (2 mg;  $n = 38$ ) was compared to ziprasidone (20 mg;  $n = 41$ ) for the acute control of agitated psychotic patients (Daniel et al. 2001). The study found that the mean BARS score decreased significantly in the 20-mg dose group compared to the 2-mg dose treatment from 15 min after the first injection until at least 4 h ( $P < 0.001$ ). In both trials all ziprasidone doses were very well tolerated and no differences were found regarding AE between the different treatment doses (Daniel et al. 2001; Lesem et al. 2001). Different doses of ziprasidone were also assessed in a 24-h, randomised, double-blind trial that compared ziprasidone 2–8 mg ( $n = 38$ ) and 20–80 mg ( $n = 41$ ) in 79 agitated psychotic inpatients (Agid et al., 2008). Ziprasidone (20 mg) was associated with a greater and more rapid decrease in the PANSS-EC scores at 4 h after the first injection compared to ziprasidone (2 mg;  $P = 0.02$ ), and this greater improvement was maintained through (24 h;  $P = 0.06$ ).

In a multisite, open-label, phase IIIb non-comparative trial of 150 acutely agitated schizophrenic patients, the effectiveness of i.m. ziprasidone was assessed during 3 days. According to the BARS, i.m. ziprasidone was effective in the management of agitation and lead to a rapid response (approximately 3 h after first injection of ziprasidone). About one out of four patients experienced mild to moderate AEs, with the most frequent being psychiatric or cardiovascular in nature (Mautone et al. 2011).

**Intravenous formulations.** Six studies of intravenous (i.v.) treatment for agitation were identified, all involving comparisons between droperidol monotherapy and a BZD (Richards et al. 1997, 1998; Knott et al. 2006), placebo (Rosen et al. 1997) or olanzapine (Chan et al. 2013) and one study comparing i.v. haloperidol to i.v. sodium valproate (Asadollahi et al. 2015) (Table 8).

In a 1-hour, randomised, open-label trial, Richards et al. (1997) compared i.v. droperidol (2.5–5 mg;  $n = 72$ ) to lorazepam (2–4 mg;  $n = 74$ ) in 146 agitated patients

with methamphetamine abuse in a randomised, prospective study. Patients receiving droperidol had significantly higher sedation scores (six-point scale) compared to i.v. lorazepam from 10 to 60 min (all,  $P < 0.001$ ). More repeated doses of lorazepam were given compared to droperidol at 30 min, and no differences were found regarding the AE profile. In a second trial with the same study design, Richards et al. (1998) compared i.v. droperidol (2.5–5 mg;  $n = 102$ ) to i.v. lorazepam (2–4 mg;  $n = 100$ ) in agitated patients presenting to an emergency department with unspecified psychosis (10%) or drug abuse (90%). Droperidol was statistically superior compared to lorazepam in terms of sedation from 10 to 60 min and onset of response (all,  $P < 0.001$ ), according to the same six-point sedation scale. There were no significant differences between the two drugs regarding AES. More recently, Knott et al. (2006) conducted a 1-h, randomised, double-blind comparison of i.v. droperidol (2.5–5 mg;  $n = 79$ ) and i.v. midazolam (2.5–5 mg;  $n = 74$ ) in 153 agitated patients with psychiatric illness or substance abuse in an emergency department. There were no differences in time to sedation despite midazolam group achieved sedation faster (6.5 min) than the droperidol group (8 min) according to a six-point sedation scale. There were no significant differences between the two drugs in AEs rates.

When i.v. droperidol (5 mg;  $n = 23$ ) has been compared to i.v. placebo ( $n = 23$ ) in a 1-day, randomised, double-blind trial with aggressive patients in a pre-hospital setting (Rosen et al. 1997), droperidol was associated with significantly greater sedation compared to placebo at 5 min ( $P = 0.05$ ) according to a five-point agitation scale with no differences regarding the AEs profile.

Intravenous droperidol (5 mg) was also compared to i.v. olanzapine (5 mg) and i.v. placebo in a multisite, randomised, double-blind, placebo-controlled trial of 336 acutely agitated patients (with mental illness and/or organic conditions which required immediate i.v. sedative containment) in an emergency department (Chan et al. 2013). All treatment arms received also immediately i.v. midazolam (2.5–5 mg) until sedation was achieved according to a six-point sedation scale. Duration to adequate sedation for the droperidol and olanzapine groups was significantly shorter than that for the placebo group (21.3 vs. 14.0 vs. 67.8 min, respectively). The two active treatment groups appeared equally effective. There were no differences in the AEs profile and rates between the three treatment arms.

In a 30-min prospective, randomised, double-blind trial, Asadollahi et al. (2015) compared i.v. sodium valproate (200 ml;  $n = 80$ ) solution *plus* placebo solution

Table 8. Included studies with intravenous formulations for the pharmacological management of agitation.

Study	Design	Population	Interventions	Agitation outcomes
Asadollahi et al. (2015)	RCT, double-blind. 30 min.	$N = 160$ Agitation in undifferentiated psychiatric illness (psychotic disorders, mood disorders, cognitive impairment, adjustment disorders, and unknown aetiology).	(1) Haloperidol i.v. (5 mg) plus placebo i.v. ( $n = 80$ ) (2) Sodium valproate i.v. (200 ml) plus placebo i.v. ( $n = 80$ )	PANSS-EC, ABS and ACES at 30 min: No differences between treatment groups in the PANSS-EC and ABS. ACES at 30 min was larger in the valproate group ( $P = 0.028$ ).
Richards et al. (1997)	Randomised, OL. 1 h.	$N = 146$ . Agitation in methamphetamine abuse.	(1) Droperidol i.v. 2.5–5 mg ( $n = 72$ ) (2) Lorazepam i.v. 2–4 mg ( $n = 74$ )	Sedation score (6 points): Droperidol sedation scores were significantly better than lorazepam from 10 to 60 min ( $P < 0.001$ ).
Rosen et al. (1997)	RCT, double-blind. 24 h.	$N = 46$ . Agitation in combative patients. Pre-hospital setting.	(1) Droperidol i.v. 5 mg ( $n = 23$ ) (2) Placebo i.v. ( $n = 23$ )	Sedation score (5 points): Droperidol improvement was significantly greater compared with placebo ( $P = 0.05$ ).
Richards et al. (1998)	Phase III, RCT, double-blind, placebo-controlled, parallel-group, multisite. 24 h.	$N = 202$ . Agitation in the emergency department with unspecified psychosis or drug abuse.	(1) Droperidol i.v. 2.5–5 mg ( $n = 102$ ) (2) Lorazepam i.v. 2–4 mg ( $n = 100$ )	Sedation score (6 points): Time interval comparison demonstrated droperidol to result in significantly greater sedation at times 10, 15, 30, 60 min ( $P < 0.001$ )
Knott et al. (2006)	RCT, double-blind. 1 h.	$N = 153$ . Agitation in psychiatric illness or substance abuse. Emergency department.	(1) Droperidol i.v. 2.5–5 mg ( $n = 79$ ) (2) Midazolam 2.5–5 mg ( $n = 74$ )	Sedation score (6 points): No differences between treatments were found.
Chan et al. (2013)	RCT, double-blind, placebo-controlled, multisite. Until sedation.	$N = 336$ . Agitation that requires iv sedation suffering undifferentiated psychiatric illness and organic conditions. Emergency department.	(1) Droperidol i.v. (5 mg) plus midazolam i.v. (2.5 to 5 mg) ( $n = 112$ ) (2) Olanzapine i.v. (5 mg) plus midazolam i.v. (2.5 to 5 mg) ( $n = 109$ ) (3) Placebo i.v. plus midazolam i.v. (2.5 to 5 mg) ( $n = 115$ )	Time to sedation: Droperidol and olanzapine were faster in achieving sedation than the placebo group. No differences between the two active treatments were found.

OL, Open Label; RCT, Randomised Controlled Trial; i.v., intravenous; ABS, Agitated Behaviour Scale; ACES, Agitation and Calmness Evaluation Scale; PANSS-EC, Positive and Negative Syndrome Scale – Excited Component.

(1 ml normal saline) with i.v. haloperidol (5 mg/1 ml;  $n = 80$ ) plus placebo infusion (200 ml normal saline) in 160 acutely agitated patients with undifferentiated psychiatric illnesses (psychotic disorders, mood disorders, cognitive impairment, adjustment disorders, and unknown aetiology). At 30 min, the mean score on the ACES scale was notably higher for the valproate group compared to haloperidol ( $P = 0.028$ ). No significant differences were observed for two additional agitation scales (PANSS-EC and the Agitated Behaviour Scale, ABS). An intense sedation was the most frequent AE in all groups (36.2% for haloperidol vs. 2.5% for valproate,  $P < 0.001$ ) but vomiting and headache occurred more frequently in the valproate group ( $P < 0.001$ ) and EPS in the haloperidol arm ( $P = 0.007$ ).

**Transdermal formulations.** Another alternative treatment recently employed for the treatment of agitation is transdermal nicotine (Table 9). Allen et al. (2011a) published the only randomised, placebo-controlled study on nicotine replacement therapy for the reduction

of agitation and aggression in 40 smoking schizophrenic patients admitted to a psychiatric emergency service (Allen et al. 2011a). The nicotine replacement group received a 21-mg nicotine transdermal patch ( $n = 20$ ), while the other 20 patients were treated with a placebo patch ( $n = 20$ ). The mean Agitated Behaviour Scale (ABS) scores at 4 and 24 h significantly decreased in the nicotine group compared to the placebo. Moreover, the nicotine replacement group had a greater reduction in agitation according to the PANSS-EC scores compared to the placebo group at 4 h ( $P = 0.006$ ) and at 24 h ( $P = 0.014$ ).

**Inhaled formulations.** The latest innovation in the management of agitation is the introduction of inhaled formulations, which provide an ultra-rapid onset of action (Popovic et al. 2015). A rapid onset of action is highly desirable in the management of agitation. Traditionally, intramuscular formulations have been preferred before these new formulations became available. In this context, an inhalable formulation of loxapine

Table 9. Included studies of new formulations for the pharmacological management of agitation.

Study	Design	Population	Interventions	Agitation outcomes
Allen et al. (2011b)	Phase III, RCT, double-blind, placebo-controlled, parallel-group, multisite. 24 h.	<i>N</i> = 129. Agitation in schizophrenia, schizophreniform and schizoaffective disorder. Inpatients and psychiatric emergency services.	(1) Loxapine inh 5 mg ( <i>n</i> = 45) (2) Loxapine inh 10 mg ( <i>n</i> = 41) (3) Placebo inh ( <i>n</i> = 43)	Onset of action and PANSS-EC at 2 h: Anti-agitation effect observed at 20 min for loxapine 10-mg group treatments according to statistically significant change from baseline on the PANSS-EC as compared to placebo ( <i>P</i> = 0.002).
Lesem et al. (2011)	Phase III, RCT, double-blind, placebo-controlled, parallel-group, multisite. 24 h.	<i>N</i> = 344. Agitation in schizophrenia. Inpatient.	(1) Loxapine inh 5 mg ( <i>n</i> = 115) (2) Loxapine inh 10 mg ( <i>n</i> = 116) (3) Placebo inh ( <i>n</i> = 113)	Onset of action and PANSS-EC at 2 h: Anti-agitation effect observed at 10 min for both loxapine group treatments according to statistically significant change from baseline on the PANSS-EC as compared to placebo ( <i>P</i> < 0.0001).
Kwentus et al. (2012)	Phase III, RCT, double-blind, placebo-controlled, parallel-group, multisite. 24 h.	<i>N</i> = 314. Agitation in bipolar disorder. Inpatient.	(1) Loxapine inh 5 mg ( <i>n</i> = 104) (2) Loxapine inh 10 mg ( <i>n</i> = 105) (3) Placebo inh ( <i>n</i> = 105)	Onset of action and PANSS-EC at 2 h: Anti-agitation effect observed at 10 min for both loxapine group treatments according to statistically significant change from baseline on the PANSS-EC as compared to placebo ( <i>P</i> < 0.0001).
Allen et al. (2011a)	RCT, placebo-controlled. 24 h.	<i>N</i> = 40. Agitated patients with schizophrenia and nicotine dependence. Psychiatric emergency service.	(1) 21-mg nicotine transdermal patch plus TAU ( <i>n</i> = 20) (2) Placebo patch plus TAU ( <i>n</i> = 20)	ABS and PANSS-EC at 4 and 24 h: ABS at 4 h, 33% lower in nicotine group than in placebo, and 23% lower at 24 h. PANSS-EC improved in both groups with greater reductions in the nicotine group than the placebo group at 4 h ( <i>P</i> = 0.006) and at 24 h ( <i>P</i> = 0.014).

RCT, Randomised Controlled Trial; OL, Open Label; inh, inhaled; ABS, Agitated Behaviour Scale; PANSS-EC, Positive and Negative Syndrome Scale – Excited Component; TAU, treatment as usual.

(a FGA that shares some degree of atypicality with SGAs) has been developed (Citrome 2004, 2012). Inhaled loxapine has the benefit of a lung absorption with a rapid transition to the systemic circulation, providing an intravenous-like pharmacokinetic (Citrome 2004, 2012). Moreover, inhaled loxapine has also been shown to be effective for reducing agitation (Ng and Zeller 2010).

The review of the literature reported three trials (Allen et al. 2011b; Lesem et al. 2011; Kwentus et al. 2012) supporting the efficacy of inhaled loxapine vs. placebo in the management of acute agitation (Table 9). To our knowledge, there are no publications of trials that compared loxapine with another active medication in the management of psychomotor agitation; there are some ongoing trials comparing loxapine to midazolam and aripiprazole with no results reported to date.

Allen et al. (2011b) performed a randomised, double-blind, placebo-controlled study in 129 agitated patients with schizophrenia and schizoaffective disorder where

inhaled loxapine (5 or 10 mg single dose) was compared to placebo in the management of agitation. Loxapine (10 mg) was significantly superior to placebo according to the PANSS-EC from 20 min through to 2 h (*P* = 0.002), and both doses of loxapine were also superior to placebo on the CGI-I at 2 h (*P* < 0.05). In a Phase III multisite, randomised, double-blind, parallel-group, controlled trial that aimed to compare inhaled loxapine 5 or 10 mg with placebo in 342 agitated schizophrenic inpatients, both loxapine doses were more effective and had a faster onset than placebo according to the PANSS-EC mean change at all-time points measured in the trial (Lesem et al. 2011). With a similar study design, Kwentus et al. (2012) evaluated the efficacy of inhaled loxapine 5 or 10 mg vs. placebo in 314 bipolar disorder inpatients with manic or mixed episodes and agitation. Loxapine was better than placebo in the same agitation outcomes, with the magnitudes of the effect sizes being generally larger for the 10-mg dose of loxapine than for the 5-mg dose (Kwentus et al. 2012). With respect to AEs in the three loxapine vs. placebo trials, the most

frequent AE in the loxapine group was dysgeusia and sedation followed by dizziness, which occurred more frequently in the 10-mg loxapine group.

### *Special subpopulations*

**Agitation during pregnancy.** There is an insufficient number of studies assessing the management and treatment of psychiatric agitation in pregnant women, and often the cohorts are too small to find differences between treatment options (D'Onofrio et al. 2010). One of the possible reasons is that physicians are reluctant to medicate pregnant agitated patients, even with short acting treatments. Moreover, there is a reluctance to conduct any controlled trials in pregnant women due to ethical and insurance issues. In an observational retrospective study of 80 pregnant women admitted to a psychiatric emergency service, 31 patients (39%) required medication for agitation. In this study, haloperidol, alone or in combination with a BZD, was the most frequently administered treatment, while risperidone was the second (Ladavac et al. 2007).

Apart from this small study, there are no clinical trials comparing the effectiveness and tolerability of different agitation treatment options during pregnancy. The only attempt to address this issue is found in the expert consensus of Allen et al. (2001). This consensus suggests the use of haloperidol alone as first-line treatment and, although no consensus was reached on second-line treatment, three agents have been suggested: BZDs alone or risperidone alone and, with less endorsement, a combination of a BZD and a FGA. On the contrary, no recommendation has been provided on the issue of agitation in pregnancy by the most recent expert consensus on agitation (Allen et al. 2005; Wilson et al. 2012). Considering the paucity of evidence on this topic, it has been suggested that clinicians should employ mainly verbal interventions in pregnant agitated patients whenever possible, and when medication is required, the minimal but effective amount of medication necessary to reduce agitation and the risk of aggression should be used (Galbally et al. 2014).

**Agitation in the elderly.** When initially assessing agitation in the elderly, agitation should be presumed to be due a delirium until proven otherwise if the mental status is altered (Nassis et al. 2006). Identifying the cause of agitation and differentiating medical from psychiatric causes is essential to perform a successful management in this population (D'Onofrio et al. 2010). If a medical aetiology has been excluded, clinicians should consider affective and anxiety disorders as the most prevalent psychiatric causes of agitation in the elderly (Chaput

et al. 2011). After an adequate assessment of the aetiology it is recommended to initially try all non-pharmacological strategies, and proceed with pharmacological and/or physical restraint only when necessary, judiciously and for a short-term period, with frequent review and close monitoring (Peisah et al. 2011). Specific treatment recommendations for agitation in the elderly are mainly derived from studies on behavioural disturbances in dementia or delirium, underlining again the lack of research on agitation in the elderly due to other psychiatric conditions. In 1998, the *Expert Consensus Guidelines for the Treatment of Agitation in Older Persons with Dementia* recommended the high potency FGAs for the management of delirium with agitation in elderly patients with dementia, with risperidone as recommended second line treatment (Alexopoulos et al. 1998). The more recent *Expert Consensus Guidelines on Using Antipsychotics in Older Patients* gave preference to risperidone for treating delirium in the elderly (Alexopoulos et al. 2005), despite the FDA and EMA Black Box warnings of an increased risk of cerebrovascular incidents in older patients with long term SGA exposure (Gill et al. 2005).

As a general principle of the pharmacological treatment of the psychiatric agitation in the elderly, a cautious use of antipsychotics has been recommended: to start with low doses and slow titration with small increments of dose, to perform an appropriate observation of the medication effects and close meshed monitoring of the clinical situation, the risks of falls, signs of confusion and of over-sedation (Marder 2006; Peisah et al. 2011). According to the expert consensus of Allen et al. (2005), the first line-treatment of non-delirious agitation in the elderly should consider non-pharmacological strategies. Second-line treatments to consider involve pharmacological approaches with antipsychotics (risperidone, haloperidol, and olanzapine). At the same time BZDs should be avoided in agitated elderly patients due to safety and tolerability issues (Allen et al. 2005).

### **Discussion**

This extensive and systematic review is the basis for a number of expert-consensus-based recommendations that are listed in Table 1. Based on the review, we can state that psychomotor agitation is a frequent condition in both medical and psychiatric emergency settings (Yildiz et al. 2003; Battaglia 2005; Nordstrom et al. 2012). It has been described as a continuum from anxiety to agitation and aggression (Zeller and Rhoades 2010). In order to perform an adequate assessment of psychomotor agitation it is extremely important to rule out any

possible medical condition. Once a medical condition has been excluded and a psychiatric condition appears likely, some specific rating scales have been developed to assess these patients. The nine assessment tools reviewed here vary substantially in their suitability for use in different settings (hospital, emergency services, etc.) and their effort. Moreover, all scales inform only about the patient's condition at a given time, but the severity of agitation may change over time.

Appropriate management of agitation is of utmost importance. Despite the lack of controlled studies comparing different non-pharmacological interventions, current guidelines on the topic recommend the first line use of verbal de-escalation techniques due to their potential to decrease agitation and reduce the risk of associated violence (NICE Guidelines 2005; Knox and Holloman 2012; Richmond et al. 2012; Hasan et al. 2012; Kasper et al. 2013).

Whenever verbal techniques (or even pharmacological treatments) fail, physical restraint or seclusion may be considered but constitutes a "treatment-of-last-resort" (Marder 2006; The Joint Commission 2000). It is indicated to prevent harm to the patient and/or staff and should only be employed in the least restrictive manner possible and for the least amount of time. In these cases, a close monitoring performed by trained staff is mandatory in order to assess response to medication and to prevent complications.

Regarding pharmacological treatments, the findings from this review suggest that lorazepam and haloperidol continue to be effective treatment choices (Battaglia 2005). However, with the emergence of SGAs, the expert consensus-based guidelines (Allen et al. 2001, 2005; WFSBP 2012; Kasper et al. 2013; and BETA group) preferentially recommend SGA as first-line therapy. However, there seems to be no real difference in efficacy between SGA and FGA, both when used by its own or in combination with lorazepam (Gault et al. 2012). Oral, sublingual and inhaled formulations have been recommended (Allen et al. 2001, 2005; Kasper et al. 2013 and BETA group) as a first choice as i.m. and i.v. applications may devastate the therapeutic relationship. Only a small number of clinical trials can be considered as solid evidence in the management of agitation, and there are also concerns about the informed consent process. "Real world" agitated patients are seldom able or willing to consent to a controlled trial, thus the data from selected samples are difficult to generalise.

Concerning oral SGAs, olanzapine has the largest number of positive trials, being as effective as haloperidol (Kinon et al. 2001, 2004; Villari et al. 2008; Hsu et al. 2010; Walther et al. 2014). Regarding the dosage, oral olanzapine in flexible dose (up to 40 mg/day) performed

better in the management of agitation than a fixed dose of 10 mg with no more adverse events reported (Baker et al. 2003). For risperidone, the current literature did not support superiority over any other antipsychotic (Normann et al. 2006; Lim et al. 2010; Hsu et al. 2010) both for the ODT administration and the OS formulation (Hatta et al. 2008). Oral aripiprazole has been compared to placebo with positive results (Marder et al. 2007), while it was equally effective as oral olanzapine (Kinon et al. 2008). Oral quetiapine was superior to placebo in three trials (Chengappa et al. 2003; Vieta et al. 2005) but not superior to haloperidol (Chengappa et al. 2003), and asenapine was also better than placebo in the management of agitation (Pratts et al. 2014). No high quality trials of oral BZD on monotherapy were found.

When oral combinations were studied, the combination of FGAs (haloperidol *plus* levomepromazine) was superior to oral haloperidol monotherapy (Higashima et al. 2004). The combination of oral risperidone *plus* lorazepam was as effective as haloperidol *plus* lorazepam in three trials (Currier and Simpson 2001; Currier et al. 2004; Veser et al. 2006), but better than i.m. lorazepam (Veser et al. 2006). Another oral combination showing a similar efficacy as i.m. haloperidol alone was risperidone OS *plus* clonazepam (Fang et al. 2012). Treatment of aggression with quetiapine in combination with lithium/divalproex was more effective than placebo *plus* lithium/divalproex in another trial (Yatham et al. 2004).

For intramuscular treatments, BZDs have been compared to i.m. haloperidol in several trials. Intramuscular lorazepam was as effective as i.m. haloperidol in the majority of studies (Lenox et al. 1992; Battaglia et al. 1997; Nobay et al. 2004). Regarding other BZDs, i.m. clonazepam and i.m. flunitrazepam were equally effective as i.m. haloperidol (Chouinard et al. 1993; Dorevitch et al. 1999). Intramuscular midazolam was superior to i.m. haloperidol alone or in combination (Huf et al. 2002; TREC 2003; Nobay et al. 2004) and equally effective as i.m. droperidol (Martel et al. 2005; Isbister et al. 2010). Finally, when BZDs have been compared to SGA, they were inferior to i.m. olanzapine (Meehan et al., 2001) but as effective as i.m. aripiprazole (Zimbroff et al. 2007).

For intramuscular FGAs, droperidol appears more effective than haloperidol (Resnick & Burton 1984), but equally effective as midazolam (Isbister et al. 2010). In addition, i.m. haloperidol was not superior to chlorpromazine in the only trial found in our literature search (Man and Chen 1973). When intramuscular FGA have been compared to SGA, neither haloperidol nor droperidol were superior to i.m. olanzapine (Wright et al. 2001; Breier et al. 2002; Wilhelm et al. 2008; Castle et al. 2009;

Chandrasena et al. 2009; Hsu et al. 2010; MacDonald et al. 2010, 2012; Leung et al. 2011; Baldaçara et al. 2011; Chan et al. 2014; Suzuki et al. 2014). Results were similar when i.m. haloperidol was compared to i.m. aripiprazole (Andrezina et al. 2006a; Tran-Johnson et al. 2007; Daniel et al. 2007) or i.m. ziprasidone (Brook et al. 2000 and 2005; Preval et al. 2005; Zhang et al. 2013).

On the topic of i.m. SGAs, several trials have evaluated olanzapine. In five of them, olanzapine was more effective than placebo (Wright et al. 2001; Meehan et al. 2001; Breier et al. 2002; Katagiri et al. 2013; Chan et al. 2014). In one study, it was more effective than i.m. lorazepam (Meehan et al. 2001). Intramuscular aripiprazole was more effective than placebo in the 4 trials reviewed (Andrezina et al. 2006a; Tran-Johnson et al. 2007; Daniel et al. 2007; Zimbroff et al. 2007) and it was equally effective to lorazepam in another trial (Zimbroff et al. 2007). Regarding i.m. ziprasidone, ziprasidone 10 or 20 mg was more effective than 2 mg (Lesem et al. 2001; Daniel et al. 2001; Agid et al. 2008).

For i.m. combinations, haloperidol *plus* promethazine was more efficacious than haloperidol alone (Huf et al. 2007) or lorazepam alone (Alexander 2004). However, no differences were found when compared to midazolam alone (Huf et al. 2002) or olanzapine alone (Raveendran et al. 2007). The combination of haloperidol *plus* BZDs was as efficacious as olanzapine alone and better than haloperidol alone in two trials (MacDonald 2010, 2012) and better than lorazepam alone in another two trials (Battaglia et al. 1997; Bieniek et al. 1998).

When i.v. treatments were tested, i.v. droperidol has the largest number of trials, being superior to i.v. lorazepam and placebo for sedation (Richards et al. 1997, 1998; Rosen et al. 1997; Chan et al. 2013) and equally effective to i.v. midazolam (Knott et al. 2006). When compared to olanzapine, both treatments were equally effective (Chan et al. 2013). There is only one trial comparing i.v. haloperidol to sodium valproate in the management of agitation, with the result that both treatment were effective (Asadollahi et al. 2015).

Concerning the new aerosolized inhaled formulation of loxapine, loxapine was superior to placebo in the management of agitation in all studies reported (Allen et al. 2011a, 2011b; Lesem et al. 2011; Kwentus et al. 2012). Comparative, active-controlled trials are currently ongoing (Popovic et al. 2015).

Based on the findings from the clinical studies listed above, the available evidence dealing with the assessment and the management of psychomotor agitation is remarkably limited, and sometimes methodologically weak. Despite the fact contemporary guidelines have been developed to help clinicians in the decision making

process, it is not currently possible to make very specific clinical recommendations that are soundly evidence based. For these reasons, the intention of this expert consensus is to ascertain, as far as possible, the best management approach to patients with psychomotor agitation in psychiatric settings. No simple guidelines can be provided at this time, but clinicians are encouraged to consult our consensus-based recommendations (Table 1).

We strongly encourage further research to address the uncertainty concerning the optimal treatment of psychomotor agitation.

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## References

- Agid O, Kapur S, Warrington L, Loebel A, Siu C. 2008. Early onset of antipsychotic response in the treatment of acutely agitated patients with psychotic disorders. *Schizophr Res.* 102:241–248. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18495436>
- Alexander J. 2004. Rapid tranquilisation of violent or agitated patients in a psychiatric emergency setting: Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. *Br J Psychiatr.* 185:63–69. Available from: <http://bjp.rcpsych.org/cgi/doi/10.1192/bjp.185.1.63>
- Alexopoulos GS, Jeste DV, Chung H, Carpenter D, Ross R, Docherty JP. 2005. The expert consensus guideline series. Treatment of dementia and its behavioral disturbances. Introduction: methods, commentary, and summary. *Postgrad Med.* 6–22.
- Alexopoulos GS, Silver JM, Kahn DA, et al. 1998. Treatment of agitation in older persons with dementia. The Expert Consensus Panel for agitation in dementia. *Postgrad Med. Spec No:* 1–88.
- Allen MH, Currier GW. 2004. Use of restraints and pharmacotherapy in academic psychiatric emergency services. *Gen Hosp Psychiatr.* 26:42–49. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14757302>
- Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP. 2005. The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract.* 11 (Suppl 1):5–108. quiz 110–112. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16319571>
- Allen MH, Currier GW, Hughes DH, Docherty JP, Carpenter D, Ross R. 2003. Treatment of behavioral emergencies: a summary of the expert consensus guidelines. *J Psychiatr Pract.* 9:16–38. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15985913>
- Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP. 2001. The Expert Consensus guideline series. Treatment of behavioral emergencies. *Postgrad Med.* 1–88. quiz 89–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11500996>
- Allen MH, Debanné M, Lazignac C, Adam E, Dickinson LM, Damsa C. 2011a. Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: a double-blind, randomized, placebo-controlled study. *Am J Psychiatr.* 168:395–399.
- Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar P, et al. 2011b. Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: A

- randomized, double-blind, placebo-controlled trial. *J Clin Psychiatr.* 72:1313–1321.
- Almvik R, Woods P. 1999. Predicting inpatient violence using the Broset Violence Checklist (BVC). *Int J Psychiatr Nurs Res.* 4:498–505. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10451308>
- APA (American Psychiatric Association). 1987. Diagnostic and statistical manual on mental disorders, third edition-revised. Washington (DC): American Psychiatric Publishing.
- APA (American Psychiatric Association). 2013. Diagnostic and statistical manual of mental disorders, 5th edition. Washington (DC): American Psychiatric Publishing. Available from: <http://dsm.psychiatryonline.org//book.aspx?doi=10.1176/appi.books.9780890425596.893619>
- Andrezina R, Josiassen RC, Marcus RN, Oren DA, Manos G, Stock E, et al. 2006a. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)*. 106:281–292. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16953381>
- Andrezina R, Marcus RN, Oren DA, Manos G, Stock E, Carson WH, et al. 2006b. Intramuscular aripiprazole or haloperidol and transition to oral therapy in patients with agitation associated with schizophrenia: sub-analysis of a double-blind study. *Curr Med Res Opin.* 22:2209–2219. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17076982>
- Angermeyer MC. 2000. Schizophrenia and violence. *Acta Psychiatr Scand. Suppl.*63–67.
- Angst J, Gamma A, Benazzi F, Ajdacic V, Rössler W. 2009. Does psychomotor agitation in major depressive episodes indicate bipolarity? Evidence from the Zurich Study. *Eur Arch Psychiatr Clin Neurosci.* 259:55107. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18806921>
- Arvanitis LA, Miller BG. 1997. Multiple fixed doses of “Seroquel” (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry.* 42:233–246. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9270900>
- Asadollahi S, Heidari K, Hatamabadi H, Vafae R, Yunesian S, Azadbakht A, et al. 2015. Efficacy and safety of valproic acid versus haloperidol in patients with acute agitation. *Int Clin Psychopharmacol.* 30:142–150. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:land ingpage&an=00004850-201505000-00003>
- Baker SN. Management of acute agitation in the emergency department. *Adv Emerg Nurs J.* 34:306–18; quiz 319–20. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23111305>
- Baker RW, Kinon BJ, Maguire Ga, Liu H, Hill AL. 2003. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol.* 23:342–348. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12920409>
- Balázs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS. 2006. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. *J Affect Disord.* 91:133–138. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16458364>
- Baldaçara L, Sanches M, Cordeiro DC, Jackowski AP. 2011. Rapid tranquilization for agitated patients in emergency psychiatric rooms: a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. *Rev Bras Psiquiatr.* 33:30–39. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21537720>
- Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L, et al. 1997. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med.* 15:335–340. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9217519>
- Battaglia J. 2005. Pharmacological management of acute agitation. *Drugs.* 65:1207–1222. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15916448>
- Bieniek SA, Ownby RL, Penalver A, Dominguez RA. 1998. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy.* 18:57–62. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9469682>
- Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, et al. 2005. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatr.* 66:111–121.
- Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, et al. 2002. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatr.* 59:441–448. Available from: <http://archpsyc.jamanetwork.com/article.aspx?articleid=206340>
- Brook S, Lucey JV, Gunn KP. 2000. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatr.* 61:933–941. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11206599>
- Brook S, Walden J, Benattia I, Siu CO, Romano SJ. 2005. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology (Berl)*. 178:514–523. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15650846>
- Bryan CJ, Hitschfeld MJ, Palmer BA, Schak KM, Roberge EM, Lineberry TW. 2014. Gender differences in the association of agitation and suicide attempts among psychiatric inpatients. *Gen Hosp Psychiatr.* 36:726–731. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25312276>
- Buchanan A, Leese M. 2001. Detention of people with dangerous severe personality disorders: a systematic review. *Lancet* 358:1955–1959. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11747920>
- Castle DJ, Udristoiu T, Kim CY, Sarosi A, Pidrman V, Omar AN, et al. 2009. Intramuscular olanzapine versus short-acting typical intramuscular antipsychotics: comparison of real-life effectiveness in the treatment of agitation. *World J Biol Psychiatr.* 10:43–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19137460>
- Chan EW, Taylor DM, Knott JC, Kong DCM. 2011. Variation in the management of hypothetical cases of acute agitation in Australasian emergency departments. *Emerg Med Australas.* 23:23120. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21091874>
- Chan EW, Taylor DM, Knott JC, Phillips GA, Castle DJ, Kong DCM. 2013. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: A

- multicenter, randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med.* 61:72–81.
- Chan H-Y, Ree S-C, Su L-W, Chen J-J, Chou S-Y, Chen C-K, et al. 2014. A double-blind, randomized comparison study of efficacy and safety of intramuscular olanzapine and intramuscular haloperidol in patients with schizophrenia and acute agitated behavior. *J Clin Psychopharmacol.* 34:355–358. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24743717>
- Chandrasena R, Dvoráková D, Lee SI, Loza N, Mosolov SN, Osváth P, et al. 2009. Intramuscular olanzapine vs. intramuscular short-acting antipsychotics: safety, tolerability and the switch to oral antipsychotic medication in patients with schizophrenia or acute mania. *Int J Clin Pract.* 63:1249–1258. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19558486>
- Chaput Y, Beaulieu L, Paradis M, Labonté E. 2011. The elderly in the psychiatric emergency service (PES); a descriptive study. *BMC Psychiatr.* 11:111
- Chengappa KNR, Goldstein JM, Greenwood M, John V, Levine J. 2003. A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. *Clin Ther.* 25:530–541. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12749512>
- Chouinard G, Annable L, Turnier L, Holobow N, Szkrumelak N. 1993. A double-blind randomized clinical trial of rapid tranquilization with I.M. clonazepam and I.M. haloperidol in agitated psychotic patients with manic symptoms. *Can J Psychiatr.* 38 (Suppl 4):S114–S121. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8306241>
- Citrome L. 2002. Atypical antipsychotics for acute agitation. New intramuscular options offer advantages. *Postgrad Med.* 112:85–88. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12510449>
- Citrome L. 2004. New treatments for agitation. *Psychiatr Q.* 75:197–213. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15335224>
- Citrome L. 2012. Inhaled loxapine for agitation revisited: Focus on effect sizes from 2 Phase III randomised controlled trials in persons with schizophrenia or bipolar disorder. *Int J Clin Pract.* 66:318–325.
- Citrome L, Volavka J. 2014. The psychopharmacology of violence: making sensible decisions. *CNS Spectr.* 19:411–418. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24571828>
- Cohen-Mansfield J, Werner P, Marx MS. 1989. An observational study of agitation in agitated nursing home residents. *Int Psychogeriatr.* 1:153–165. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2491142>
- Cooper SJ, Browne FW, McClean KJ, King DJ. 1983. Aggressive behaviour in a psychiatric observation ward. *Acta Psychiatr Scand.* 68:386–393. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6650217>
- Cornaggia CM, Beghi M, Pavone F, Barale F. 2011. Aggression in psychiatry wards: A systematic review. *Psychiatr Res.* 189:10–20. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21236497>
- Currier GW, Allen MH, Bunney EB, Daniel DG, Francis A, Jagoda A, et al. 2004. Standard therapies for acute agitation. *J Emerg Med.* 27:S9–12. quiz S7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15504618>
- Currier GW, Citrome LL, Zimbroff DL, Oren D, Manos G, McQuade R, et al. 2007. Intramuscular aripiprazole in the control of agitation. *J Psychiatr Pract.* 13:159–169. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17522559>
- Currier GW, Medori R. 2006. Orally versus intramuscularly administered antipsychotic drugs in psychiatric emergencies. *J Psychiatr Pract.* 12:30–40. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16432443>
- Currier GW, Simpson GM. 2001. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. *J Clin Psychiatr.* 62:153–157. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11305699>
- D’Onofrio G, Jauch E, Jagoda A, Allen MH, Anglin D, Barsan WG, et al. 2010. NIH roundtable on opportunities to advance research on neurologic and psychiatric emergencies. *Ann Emerg Med.* 56:551–564.
- Dack C, Ross J, Papadopoulos C, Stewart D, Bowers L. 2013. A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. *Acta Psychiatr Scand.* 127:255–268. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23289890>
- Daniel DG, Currier GW, Zimbroff DL, Allen MH, Oren D, Manos G, et al. 2007. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. *J Psychiatr Pract.* 13:170–177. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17522560>
- Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. 2001. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl).* 155:128–134. Available from: <http://link.springer.com/10.1007/s002130000658>
- Daniel DG, Saha AR, Ingenito GCW, GD. 2000. Aripiprazole, a novel antipsychotic: overview of a phase II study result [abstract]. *Int J Neuropsychopharmacol.* 3 (Suppl 1):S157.
- De Filippis S, Cuomo I, Lionetto L, Janiri D, Simmaco M, Caloro M, et al. 2013. Intramuscular Aripiprazole in the Acute Management of Psychomotor Agitation. *Pharmacotherapy.* 33:603–614. Available from: <http://doi.wiley.com/10.1002/phar.1260>
- Dolan M, Blattner R. 2010. The utility of the Historical Clinical Risk-20 Scale as a predictor of outcomes in decisions to transfer patients from high to lower levels of security—a UK perspective. *BMC Psychiatr.* 10:76
- Donat DC. 2003. An analysis of successful efforts to reduce the use of seclusion and restraint at a public psychiatric hospital. *Psychiatr Serv.* 54:1119–1123. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12883139>
- Dorevitch A, Katz N, Zemishlany Z, Aizenberg D, Weizman A. 1999. Intramuscular flunitrazepam versus intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. *Am J Psychiatr.* 156:142–144.
- Doyle M, Dolan M. 2006. Predicting community violence from patients discharged from mental health services. *Br J Psychiatr.* 189:520–526. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17139036>
- Duxbury J, Whittington R. 2005. Causes and management of patient aggression and violence: staff and patient perspectives. *J Adv Nurs.* 50:469–478. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15882363>
- Escobar R. 2008. Effectiveness results of olanzapine in acute psychotic patients with agitation in the emergency room

- setting: results from NATURA study. *Actas Esp Psiquiatr.* 36:151–157.
- Fang M, Chen H, Li L-H, Wu R, Li Y, Liu L, et al. 2012. Comparison of risperidone oral solution and intramuscular haloperidol with the latter shifting to oral therapy for the treatment of acute agitation in patients with schizophrenia. *Int Clin Psychopharmacol.* 27:107–113. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22233697>
- Fisher WA. 1994. Restraint and seclusion: a review of the literature. *Am J Psychiatry.* 151:1584–1591. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7943445>
- Fishkind A. 2002. Calming agitation with words, not drugs: 10 commandments for safety. *Curr Psych.* 1(4).
- Fitzgerald CH. 1969. A double-blind comparison of haloperidol with perphenazine in acute psychiatric episodes. *Curr Ther Res Clin Exp.* 11:515–519.
- Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 12:189–198. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1202204>
- Ford AH, Almeida OP. 2015. Pharmacological interventions for preventing delirium in the elderly. *Maturitas.* 81:287–292. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25890587>
- Fountoulakis KN, Leucht S, Kaprinis GS. 2008. Personality disorders and violence. *Curr Opin Psychiatr.* 21:84–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18281846>
- Fresán A, Apiquian R, de la Fuente-Sandoval C, García-Anaya M, Nicolini H. [Sensitivity and specificity of the Overt Aggression Scale in schizophrenic patients]. *Actas Españolas Psiquiatr.* 32:71–75. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15042466>
- Fruensgaard K, Korsgaard S, Jorgensen H, Jensen K. 1977. Loxapine versus haloperidol parenterally in acute psychosis with agitation. A double-blind study. *Acta Psychiatr Scand.* 56:256–264.
- Galbally M, Snellen M, Power J. 2014. Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. *Ther Adv Drug Saf.* 5:100–109. Available from: <http://taw.sagepub.com/content/5/2/100.abstract>
- Gault TI, Gray SM, Vilke GM, Wilson MP. 2012. Are oral medications effective in the management of acute agitation? *J Emerg Med.* 43:854–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22541877>
- Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N, et al. 2005. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 330:445. doi:10.1136/bmj.38330.470486.8F
- Gutheil TG. 1980. Restraint versus treatment: seclusion as discussed in the Boston State Hospital case. *Am J Psychiatr* 137:718–719. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7377394>
- Hankin C, Bronstone A, Koran L. 2011. Agitation in the inpatient psychiatric setting: A Review of Clinical Presentation, Burden, and Treatment. *J Psychiatr.* 17:170–185. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21586995>
- Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, et al. 2012. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatr.* 13:318–378.
- Hatta K, Kawabata T, Yoshida K, Hamakawa H, Wakejima T, Furuta K, et al. 2008. Olanzapine orally disintegrating tablet vs. risperidone oral solution in the treatment of acutely agitated psychotic patients. *Gen Hosp Psychiatr.* 30:367–371. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18585542>
- Herrera JN, Sramek JJ, Costa JF, Roy S, Heh CW, Nguyen BN. 1988. High potency neuroleptics and violence in schizophrenics. *J Nerv Ment Dis.* 176:558–561. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3418329>
- Higashima M, Takeda T, Nagasawa T, Hirao N, Oka T, Nakamura M, et al. 2004. Combined therapy with low-potency neuroleptic levomepromazine as an adjunct to haloperidol for agitated patients with acute exacerbation of schizophrenia. *Eur Psychiatr.* 19:380–381. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15363480>
- Hill S, Petit J. 2000. The violent patient. *Emerg Med Clin North Am.* 18:301–315. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10767886>
- Holloman GH, Zeller SL. 2012. Overview of Project BETA: Best practices in evaluation and treatment of agitation. *West J Emerg Med.* 13:1–2. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3298232&tool=pmc.entrez&rendertype=abstract>
- Hsu W-Y, Huang S-S, Lee B-S, Chiu N-Y. 2010. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. *J Clin Psychopharmacol.* 30:230–234. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20473056>
- Huber CG, Lambert M, Naber D, Schacht A, Hundemer H-P, Wagner TT, et al. 2008. Validation of a Clinical Global Impression Scale for Aggression (CGI-A) in a sample of 558 psychiatric patients. *Schizophr Res.* 100:342–348. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18255271>
- Huf G, Alexander J, Allen MH. 2005. Haloperidol plus promethazine for psychosis induced aggression. *Cochrane Database Syst Rev.* 1:CD005146. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15654706>
- Huf G, Coutinho ESF, Adams CE, TREC-Rio trial. 2002. TREC-Rio trial: a randomised controlled trial for rapid tranquillisation for agitated patients in emergency psychiatric rooms [ISRCTN44153243]. *BMC Psychiatr.* 2:11 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12383353>
- Huf G, Coutinho ESF, Adams CE. 2007. Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. *BMJ* 335:869 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2043463&tool=pmcentrez&rendertype=abstract>
- Hughes DH. 1996. Suicide and violence assessment in psychiatry. *Gen Hosp Psychiatr.* 18:416–421. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8937907>
- Ilkiw-Lavalle O, Grenyer BFS. 2003. Differences between patient and staff perceptions of aggression in mental health units. *Psychiatr Serv.* 54:389–393. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12610249>
- Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. 2010. Randomized controlled trial of intramuscular

- droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med.* 56:392–401.e1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20868907>
- Iwanami T, Maeshima H, Baba H, Satomura E, Namekawa Y, Shimano T, et al. 2014. Psychomotor agitation in major depressive disorder is a predictive factor of mood-switching. *J Affect Disord.* 170:185–189. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25248024>
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 17:1–12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8721797>
- Jarema M.R. 2015. Leczenie pacjentów pobudzonych. In: Medica V, editor. *Standardy leczenia farmakologicznego niektórych zaburzeń psychicznych.* Gdańsk. pp. 49–51.
- Jones J, Hunter D. 1995. Consensus methods for medical and health services research. *BMJ* 311:376–380. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2550437&tool=pmcentrez&rendertype=abstract>
- Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. 2002. Efficacy and Safety of Aripiprazole and Haloperidol Versus Placebo in Patients With Schizophrenia and Schizoaffective Disorder. *J Clin Psychiatry* 63:763–771.
- Kasper S, Baranyi A, Eisenburger P, Erfurth A, Ertl M, Frey R, et al. 2013. Die Behandlung der Agitation beim psychiatrischen Notfall. Konsensus-Statement - State of the art 2013. *Clin Neuropsychol Sonderausgabe.*
- Katagiri H, Fujikoshi S, Suzuki T, Fujita K, Sugiyama N, Takahashi M, et al. 2013. A randomized, double-blind, placebo-controlled study of rapid-acting intramuscular olanzapine in Japanese patients for schizophrenia with acute agitation. *BMC Psychiatr.* 13:20 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23311957>
- Kaufman DM, Zun L. 1995. A quantifiable, brief mental status examination for emergency patients. *J Emerg Med.* 13:449–456. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7594361>
- Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 13:261–276. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3616518>
- Kinon BJ, Ahl J, Rotelli MD, McMullen E. 2004. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. *Am J Emerg Med.* 22:181–186. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15138953>
- Kinon BJ, Roychowdhury SM, Milton DR, Hill AL. 2001. Effective resolution with olanzapine of acute presentation of behavioral agitation and positive psychotic symptoms in schizophrenia. *J Clin Psychiatr.* 62 (Suppl 2):17–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11232746>
- Kinon BJ, Stauffer VL, Kollack-Walker S, Chen L, Sniadecki J. 2008. Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. *J Clin Psychopharmacol.* 28:601–607. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19011427>
- Knott JC, Taylor DM, Castle DJ. 2006. Randomized clinical trial comparing intravenous midazolam and droperidol for sedation of the acutely agitated patient in the emergency department. *Ann Emerg Med.* 47:61–67.
- Knox DK, Holloman GH. 2012. Use and avoidance of seclusion and restraint: consensus statement of the American Association for Emergency Psychiatry Project Beta Seclusion and Restraint Workgroup. *West J Emerg Med.* 13:35–40. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3298214&tool=pmcentrez&rendertype=abstract>
- Kopecky HJ, Kopecky CR, Yudofsky SC. 1998. Reliability and validity of the Overt Agitation Severity Scale in adult psychiatric inpatients. *Psychiatr Q.* 69:301–323. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9793109>
- Kwentus J, Riesenberger RA, Marandi M, Manning RA, Allen MH, Fishman RS, et al. 2012. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disord.* 14:31–40. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22329470>
- Ladavac AS, Dubin WR, Ning A, Stuckeman PA. 2007. Emergency management of agitation in pregnancy. *Gen Hosp Psychiatr.* 29:39–41.
- Långström N, Grann M, Ruchkin V, Sjöstedt G, Fazel S. 2009. Risk factors for violent offending in autism spectrum disorder: a national study of hospitalized individuals. *J Interpers Violence* 24:1358–1370. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18701743>
- Lee HK, Villar O, Juthani N, Bluestone H. 1989. Characteristics and behavior of patients involved in psychiatric ward incidents. *Hosp Community Psychiatr.* 40:1295–1297. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2591887>
- Lenox RH, Newhouse PA, Creelman WL, Whitaker TM. 1992. Adjunctive treatment of manic agitation with lorazepam versus haloperidol: a double-blind study. *J Clin Psychiatr.* 53:47–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1541605>
- Lesem MD, Tran-Johnson TK, Riesenberger RA, Feifel D, Allen MH, Fishman R, et al. 2011. Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. *Br J Psychiatr.* 198:51–58. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21200077>
- Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. 2001. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatr.* 62:12–18. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11235922>
- Lesser JM, Hughes S. 2006. Psychosis-related disturbances. Psychosis, agitation, and disinhibition in Alzheimer's disease: definitions and treatment options. *Geriatrics.* 61:14–20. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17184138>
- Leung JG, Benedetti AM, Frazee LA, Myers N. 2011. Comparison of short-acting intramuscular antipsychotic medication: impact on length of stay and cost. *Am J Ther.* 18:300–304. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20335789>
- Lim HK, Kim JJ, Pae CU, Lee CU, Lee C, Paik IH. 2010. Comparison of risperidone orodispersible tablet and intramuscular haloperidol in the treatment of acute psychotic agitation: a randomized open, prospective study. *Neuropsychobiology.* 62:81–86. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20523078>
- Linaker OM, Busch-Iversen H. 1995. Predictors of imminent violence in psychiatric inpatients. *Acta Psychiatr Scand.*

- 92:250–254. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8848948>
- Lindenmayer JP. 2000. The pathophysiology of agitation. *J Clin Psychiatr.* 61 (Suppl 1):5–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11154018>
- Lindenmayer J-P, Bossie CA, Kujawa M, Zhu Y, Canuso CM. 2008. Dimensions of psychosis in patients with bipolar mania as measured by the positive and negative syndrome scale. *Psychopathology.* 41:264–270. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18441528>
- Lukens TW, Wolf SJ, Edlow Ja, Shahabuddin S, Allen MH, Currier GW, et al. 2006. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med.* 47:79–99. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16387222>
- MacDonald K, Wilson M, Minassian A, Vilke GM, Becker O, Tallian K, et al. 2012. A naturalistic study of intramuscular haloperidol versus intramuscular olanzapine for the management of acute agitation. *J Clin Psychopharmacol.* 32:317–322. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22544013>
- MacDonald K, Wilson MP, Minassian A, Vilke GM, Perez R, Cobb P, et al. 2010. A retrospective analysis of intramuscular haloperidol and intramuscular olanzapine in the treatment of agitation in drug- and alcohol-using patients. *Gen Hosp Psychiatry.* 32:443–445. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20633750>
- Man PL, Chen CH. 1973. Rapid tranquilization of acutely psychotic patients with intramuscular haloperidol and chlorpromazine.
- Mantovani C, Labate CM, Sponholz A, de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, et al. 2013. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. *J Clin Psychopharmacol.* 33:306–312. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23609398>
- Marco CA, Vaughan J. 2005. Emergency management of agitation in schizophrenia. *Am J Emerg Med.* 23:767–76. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16182986>
- Marder SR. 2006. A review of agitation in mental illness: Treatment guidelines and current therapies. *J Clin Psychiatry.* 67 (Suppl 1):13–21.
- Marder SR, West B, Lau GS, Pultz JA, Pikalov A, Marcus RN, et al. 2007. Aripiprazole effects in patients with acute schizophrenia experiencing higher or lower agitation: a post hoc analysis of 4 randomized, placebo-controlled clinical trials. *J Clin Psychiatry.* 68:662–668. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17503974>
- Martel M, Sterzinger A, Miner J, Clinton J, Biro M. 2005. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med.* 12:1167–1172. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16282517>
- Mautone A Scarone S., all investigators. 2011. Transition from ziprasidone im to oral formulation in agitated patients with acute exacerbation of schizophrenia: an open trial. *Pharmacopsychiatry.* 44:173–178. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21751127>
- McClure JR, Criqui MH, Macera CA, Ji M, Nievergelt CM, Zisook S. 2015. Prevalence of suicidal ideation and other suicide warning signs in veterans attending an urgent care psychiatric clinic. *Compr Psychiatry.* 60:149–155. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0010440X14002661>
- McEvoy JP, Daniel DG, Carson WH, McQuade RD, Marcus RN. 2007. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. *J Psychiatr Res.* 41:895–905.
- McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J. 2005. Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol.* 15:573–585.
- McNiel DE, Binder RL. 1994. The relationship between acute psychiatric symptoms, diagnosis, and short-term risk of violence. *Hosp Community Psychiatr.* 45:133–137. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8168791>
- Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, et al. 2001. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol.* 21:389–397. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11476123>
- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. 2015. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 4:1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25554246>
- Mohr WK, Petti TA, Mohr BD. 2003. Adverse effects associated with physical restraint. *Can J Psychiatr.* 48:330–337. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12866339>
- Montoya A, Valladares A, Lizán L, San L, Escobar R, Paz S. 2011. Validation of the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC) in a naturalistic sample of 278 patients with acute psychosis and agitation in a psychiatric emergency room. *Health Qual Life Outcome.* 9:18 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3078838&tool=pmcentrez&rendertype=abstract>
- Nassisi D, Korc B, Hahn S, Bruns J, Jagoda A. 2006. The evaluation and management of the acutely agitated elderly patient. *Mt Sinai J Med.* 73:976–984.
- Ng AT, Zeller SRR. 2010. Clinical challenges in the pharmacologic management of agitation. *Prim Psychiatr.* 18:46–52.
- Nijman HLI, Palmstierna T, Almvik R, Stolker JJ. 2005. Fifteen years of research with the staff observation aggression scale: A review. *Acta Psychiatr Scand.* 111:12–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15636589>
- Nobay F, Simon BC, Levitt MA, Dresden GM. 2004. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. *Acad Emerg Med.* 11:744–749. Available from: <http://doi.wiley.com/10.1197/j.aem.2003.06.015>
- Nordstrom K, Allen MH. 2007. Managing the acutely agitated and psychotic patient. *CNS Spectr.* 12:5–11. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17934384>

- Nordstrom K, Zun LS, Wilson MP, Md VS, Ng AT, Bregman B, et al. 2012. Medical evaluation and triage of the agitated patient: consensus statement of the american association for emergency psychiatry project Beta medical evaluation workgroup. *West J Emerg Med.* 13:3–10. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3298208&tool=pmcentrez&rendertype=abstract>
- Normann C, Schmauss M, Bakri N, Gerwe M, Schreiner A. 2006. Initial treatment of severe acute psychosis with fast orally disintegrating risperidone tablets. *Pharmacopsychiatry.* 39:209–212. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17124642>
- Nourse R, Reade C, Stoltzfus J, Mittal V. 2014. Demographics, clinical characteristics, and treatment of aggressive patients admitted to the acute behavioral unit of a community general hospital: a prospective observational study. *Prim Care Companion CNS Disord.* 16:ppi. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4195636&tool=pmcentrez&rendertype=abstract>
- Ogloff JRP, Daffern M. 2006. The dynamic appraisal of situational aggression: an instrument to assess risk for imminent aggression in psychiatric inpatients. *Behav Sci Law.* 24:799–813. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17171770>
- Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. 2013. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatr.* 170:1249–1262. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4091043&tool=pmcentrez&rendertype=abstract>
- Pacchiarotti I, Mazarini L, Kotzalidis GD, Valentí M, Nivoli AMA, Sani G, et al. 2011. Mania and depression. Mixed, not stirred. *J Affect Disord.* 133:105–113. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21514674>
- Palmstierna T, Wistedt B. 1987. Staff observation aggression scale, SOAS: presentation and evaluation. *Acta Psychiatr Scand.* 76:657–663. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3442256>
- Paprocki J. 1977. A double-blind comparison between loxapine and haloperidol by parenteral route in acute schizophrenia. *Curr Ther Res Clin Exp.* 21:80–100.
- Pascual JC, Madre M, Puigdemont D, Oller S, Corripio I, Díaz A, et al. [A naturalistic study: 100 consecutive episodes of acute agitation in a psychiatric emergency department]. *Actas españolas Psiquiatr.* 34:239–44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16823684>
- Peiró S, Gómez G, Navarro M, Guadarrama I, Rejas J, Alvarez Díaz A, et al. 2004. Length of stay and antipsychotic treatment costs of patients with acute psychosis admitted to hospital in Spain - Description and associated factors - The Psychosp study. *Soc Psychiatry Psychiatr Epidemiol.* 39:507–513.
- Peisah C, Chan D, McKay R, Kurrle SE, Reutens SG. 2011. Practical guidelines for the acute emergency sedation of the severely agitated older patient. *Intern Med J.* 41:651–657.
- Perrin E, Anand E, Dyachkova Y, Wagner T, Frediani S, Ballerini A. 2012. A prospective, observational study of the safety and effectiveness of intramuscular psychotropic treatment in acutely agitated patients with schizophrenia and bipolar mania. *Eur Psychiatr.* 27:234–239. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20620029>
- Perugi G, Akiskal HS, Micheli C, Toni C, Madaro D. 2001. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. *J Affect Disord.* 67:105–114. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11869757>
- Perugi G, Angst J, Azorin J-M, Bowden CL, Mosolov S, Reis J, et al. 2015. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatr.* 76:e351–e358. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25830457>
- Petit JR. 2005. Management of the acutely violent patient. *Psychiatr Clin North Am.* 28:701–711, 710. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16122575>
- Piechniczek-Buczek J. 2006. Psychiatric emergencies in the elderly population. *Emerg Med Clin North Am.* 24:467–490. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16584967>
- Pilowsky LS, Ring H, Shine PJ, Battersby M, Lader M. 1992. Rapid tranquillisation. A survey of emergency prescribing in a general psychiatric hospital. *Br J Psychiatry.* 160:831–835. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1352166>
- Popovic D, Nuss P, Vieta E. 2015. Revisiting loxapine: A systematic review. *Ann Gen Psychiatr.* 14:15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25859275>
- Popovic D, Vieta E, Azorin J-M, Angst J, Bowden CL, Mosolov S, et al. 2015. Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disord.* 17:795–803. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26415692>
- Potkin SG, Saha MD, PhD AR, Kujawa MJ, PhD MD, Carson WH, et al., 2003. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatr.* 60:681–690.
- Powell G, Caan W, Crowe M. 1994. What events precede violent incidents in psychiatric hospitals? *Br J Psychiatry.* 165:107–112. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7953012>
- Powney MJ, Adams CE, Jones H. 2012. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). *Cochrane database Syst Rev.* 11:CD009377. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23152276>
- Pratts M, Citrome L, Grant W, Leso L, Opler LA. 2014. A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta Psychiatr Scand.* 130:61–68. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24606117>
- Preval H, Klotz SG, Southard R, Francis A. 2005. Rapid-acting IM ziprasidone in a psychiatric emergency service: a naturalistic study. *Gen Hosp Psychiatr.* 27:140–144. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15763126>
- Putkonen A, Kuivalainen S, Louheranta O, Repo-Tiihonen E, Ryyänen O-P, Kautiainen H, et al. 2013. Cluster-randomized controlled trial of reducing seclusion and restraint in secured care of men with schizophrenia. *Psychiatr Serv.* 64:850–855. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23771480>
- Ramadan M. 2006. Managing psychiatric emergencies. *Internet J Emerg Med.* 4: Available from: <https://ispub.com/IJEM/4/1/13551>
- Raveendran NS, Tharyan P, Alexander J, Adams CE. 2007. Rapid tranquillisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus

- promethazine. *BMJ*. 335:865. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10>
- Resnick M, Burton BT. 1984. Droperidol vs. haloperidol in the initial management of acutely agitated patients. *J Clin Psychiatr*. 45:298–299. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6376480>
- Ribeiro JD, Bender TW, Selby Ea, Hames JL, Joiner TE. 2011. Development and validation of a brief self-report measure of agitation: the Brief Agitation Measure. *J Pers Assess*. 93:597–604. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21999383>
- Richards JR, Derlet RW, Duncan DR. 1997. Methamphetamine toxicity: treatment with a benzodiazepine versus a butyrophenone. *Eur J Emerg Med*. 4:130–135.
- Richards JR, Derlet RW, Duncan DR. 1998. Chemical restraint for the agitated patient in the emergency department: Lorazepam versus droperidol. *J Emerg Med*. 16:567–573.
- Richmond JS, Berlin JS, Fishkind AB, Holloman GH, Zeller SL, Wilson MP, et al. 2012. Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. *West J Emerg Med*. 13:17–25. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3298202&tool=pmcentrez&rendertype=abstract>
- Rosen CL, Ratliff AF, Wolfe RE, Branney SW, Roe EJ, Pons PT. 1997. The efficacy of intravenous droperidol in the prehospital setting. *J Emerg Med*. 15:13–17.
- Royal College of Nursing. 2005. Violence. The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments. London: Royal College of Nursing.
- Rubio-Valera M, Luciano JV, Ortiz JM, Salvador-Carulla L, Gracia A, Serrano-Blanco A. 2015. Health service use and costs associated with aggressiveness or agitation and containment in adult psychiatric care: a systematic review of the evidence. *BMC Psychiatr*. 15:35 Available from: <http://www.biomedcentral.com/1471-244X/15/35>
- Sachs GS. 2006. A review of agitation in mental illness: burden of illness and underlying pathology. *J Clin Psychiatry*. 67(Suppl 1):5–12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16965190>
- Sachs G, Chengappa KNR, Suppes T, Mullen JA, Brecher M, Devine NA, et al. 2004. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 6:213–223.
- Sachs GS, Gaulin BD, Gutierrez-Esteinou R, McQuade RD, Pikalov A, Pultz JA, et al. 2007. Antimanic response to aripiprazole in bipolar I disorder patients is independent of the agitation level at baseline. *J Clin Psychiatr*. 68:1377–1383. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17915976>
- Sani G, Tondo L, Koukopoulos A, Reginaldi D, Kotzalidis GD, Koukopoulos AE, et al. 2011. Suicide in a large population of former psychiatric inpatients. *Psychiatr Clin Neurosci*. 65:286–295.
- Schleifer JJ. 2011. Management of acute agitation in psychosis: an evidence-based approach in the USA. *Adv Psychiatr Treat*. 17:91–100. Available from: <http://apt.rcpsych.org/cgi/doi/10.1192/apt.bp.109.007310>
- Shah A, Evans H, Parkash N. 1998. Evaluation of three aggression/agitation behaviour rating scales for use on an acute admission and assessment psychogeriatric ward. *Int J Geriatr Psychiatr*. 13:415–420. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9658278>
- Sheridan M, Henrion R, Robinson L, Baxter V. 1990. Precipitants of violence in a psychiatric inpatient setting. *Hosp Community Psychiatr*. 41:776–780. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2365311>
- Shim IH, Woo YS, Jun T-Y, Bahk W-M. 2014. Mixed-state bipolar I and II depression: time to remission and clinical characteristics. *J Affect Disord*. 152:340–346. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24144581>
- Silver JM, Yudofsky SC. 1991. The Overt Aggression Scale: Overview and guiding principles. *J Neuropsychiatry Clin Neurosci*. 3:S22–S29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1821217>
- Soyka M. 2002. Aggression in schizophrenia: assessment and prevalence. *Br J Psychiatr*. 180:278–279. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11872524>
- Stabenau JR, Grinols DR. 1964. A double-blind comparison of thioridazine and chlorpromazine. *Psychiatr Q*. 38:42–63. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14148394>
- Stevenson S, Otto MP. 1998. Finding ways to reduce violence in psychiatric hospitals. *J Healthc Qual*. 20:28–32. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10181903>
- Stotsky BA. 1977. Relative efficacy of parenteral haloperidol and thiothixene for the emergency treatment of acutely excited and agitated patients. *Dis Nerv Syst*. 38:967–973.
- Stowell KR, Florence P, Harman HJ, Glick RL. 2012. Psychiatric evaluation of the agitated patient: consensus statement of the American association for emergency psychiatry project Beta Psychiatric Evaluation Workgroup. *West J Emerg Med*. 13:11–16. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3298217&tool=pmcentrez&rendertype=abstract>
- Strout TD. 2014. Psychometric testing of the Agitation Severity Scale for acute presentation behavioral management patients in the emergency department. *Adv Emerg Nurs J*. 36:250–270. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25076401>
- Suzuki H, Gen K, Takahashi Y. 2014. A naturalistic comparison study of the efficacy and safety of intramuscular olanzapine, intramuscular haloperidol, and intramuscular levomepromazine in acute agitated patients with schizophrenia. *Hum Psychopharmacol*. 29:83–88. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24424709>
- Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. 1998. Validation of the behavioural activity rating scale (BARS): a novel measure of activity in agitated patients. *J Psychiatr Res*. 36:87–95. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11777497>
- Taymeeyapradit U, Kuasirikul S. 2002. Comparative study of the effectiveness of zuclopenthixol acetate and haloperidol in acutely disturbed psychotic patients. *J Med Assoc Thai*. 85:1301–1308.
- The Joint Commission. 2000. Joint Commission on Accreditation of Healthcare Organizations: Getting a handle on restraint: New behavioural health care standards spell out specifics of training. *Jt Comm Benchmark* 2:1–3.
- Tran-Johnson TK, Sack DA, Marcus RN, Auby P, McQuade RD, Oren DA. 2007. Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatr*. 68:111–119. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17284138>

- TREC Collaborative Group. 2003. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ*. 327:708–713. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=200800&tool=pmcentrez&rendertype=abstract>
- Tuason VB. 1986. A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. *J Clin Psychiatr*. 47:126–129.
- Veser FH, Veser BD, McMullan JT, Zealberg J, Currier GW. 2006. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis: a pilot, randomized, double-blind, placebo-controlled trial. *J Psychiatr Pract*. 12:103–108. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16728906>
- Vieta E. 2005. Mood stabilization in the treatment of bipolar disorder: focus on quetiapine. *Hum Psychopharmacol*. 20:225–236. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15880391>
- Vieta E, Grunze H, Azorin J-M, Fagiolini A. 2014. Phenomenology of manic episodes according to the presence or absence of depressive features as defined in DSM-5: Results from the IMPACT self-reported online survey. *J Affect Disord*. 156:206–213. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24439831>
- Vieta E, Mullen J, Brecher M, Paulsson B, Jones M. 2005. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Curr Med Res Opin*. 21:923–934. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15969892>
- Vieta E, Valentí M. 2013. Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. *CNS Drugs* 27:515–529. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23749421>
- Villari V, Rocca P, Fonzo V, Montemagni C, Pandullo P, Bogetto F. 2008. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. *Prog Neuropsychopharmacol Biol Psychiatr*. 32:405–413. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17900775>
- Walther S, Moggi F, Horn H, Moskvitin K, Abderhalden C, Maier N, et al. 2014. Rapid tranquilization of severely agitated patients with schizophrenia spectrum disorders: a naturalistic, rater-blinded, randomized, controlled study with oral haloperidol, risperidone, and olanzapine. *J Clin Psychopharmacol*. 34:124–128. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24346752>
- Warneke I, Rössler W, Herwig U. 2011. Does psychopathology at admission predict the length of inpatient stay in psychiatry? Implications for financing psychiatric services. *BMC Psychiatr*. 11:120
- Warren RE, Deary IJ, Frier BM. 2003. The symptoms of hyperglycaemia in people with insulin-treated diabetes: classification using principal components analysis. *Diabetes Metab Res Rev*. 19:408–414. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12951649>
- Webster, CD, Douglas, KS, Eaves, D, Hart S. 1997. HCR-20: Assessing risk for violence (Version 2). (Mental Health, Law, & Policy Institute SFU, editor.) Vancouver, Canada: MHLPI.
- Wilhelm S, Schacht A, Wagner T. 2008. Use of antipsychotics and benzodiazepines in patients with psychiatric emergencies: results of an observational trial. *BMC Psychiatr*. 8:61 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2507712&tool=pmcentrez&rendertype=abstract>
- Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. 2012. The psychopharmacology of agitation: consensus statement of the american association for emergency psychiatry project Beta psychopharmacology workgroup. *West J Emerg Med*. 13:26–34. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22461918>
- Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, et al. 2001. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatr*. 158:1149–1151. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11431240>
- Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. 2003. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *Br J Psychiatr*. 182:141–147.
- Yatham LN, Paulsson B, Mullen J, Vågerö M. 2004. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol*. 24:599–606. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004714-200412000-00004>
- Yildiz A, Sachs GS, Turgay A. 2003. Pharmacological management of agitation in emergency settings. *Emerg Med J*. 20:339–346.
- Yudofsky SC, Kopecky HJ, Kunik M, Silver JM, Endicott J. 1997. The Overt Agitation Severity Scale for the objective rating of agitation. *J Neuropsychiatry Clin Neurosci*. 9:541–548. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9447494>
- Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. 1986. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatr*. 143:35–39. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3942284>
- Zeller SL, Rhoades RW. 2010. Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clin Ther*. 32:403–425. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20399981>
- Zeller SL. 2010. Treatment of psychiatric patients in emergency settings. *Prim Psychiatr*. 17:35–41.
- Zhang H, Wang G, Zhao J, Xie S, Xu X, Shi J, et al. 2013. Intramuscular ziprasidone versus haloperidol for managing agitation in Chinese patients with schizophrenia. *J Clin Psychopharmacol*. 33:178–185. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23422376>
- Zimbroff DL, Marcus RN, Manos G, Stock E, McQuade RD, Auby P, et al. 2007. Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. *J Clin Psychopharmacol*. 27:171–176. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17414241>