

# Treatment of acute agitation in psychotic disorders

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## Abstract

Several psychotic disorders, including schizophrenia, may be associated with symptoms of acute agitation and aggression. While drug treatment of agitation is often essential, non-pharmacological interventions, both environmental and behavioral, also play important roles in the complex management of agitated patients. The most extensively used psychotropic drugs are parenteral formulas of conventional antipsychotics and benzodiazepines. Recently, injection forms of two second generation antipsychotics, olanzapine and ziprasidone, have become available. Both drugs have shown adequate efficacy and tolerability in several double-blind trials of intramuscular administration in acutely agitated psychotic patients. Compared to conventional medication, injection forms of the new antipsychotics may have a faster onset of action and more favorable profile of adverse events. Alternative approaches to injection administration include liquid drug formula, orally disintegrating tablets and wafers, treatment initiation with high doses, or rapid dose escalation. Evidence suggests that second-generation antipsychotics should be among the first-line choices in the treatment of agitation in acute psychosis.

## 1. Psychotic agitation

Agitation is a transnosological syndrome; this cluster of pathological behavior occurs in a variety of psychiatric diseases including schizophrenia, bipolar disorder, or dementia. Agitation represents a poorly organized and aimless psychomotor activity stemming from physical or mental unease [1] Motor restlessness, increased responsiveness to external or internal stimuli, irritability, inappropriate and usually purposeless verbal and motor activity are the major hallmarks of the syndrome. It can readily result into a verbal

or physical aggression toward objects or persons; the patients may then pose a danger to others [2, 3]. By definition, violence is a physical aggressive behavior that is intended to inflict harm to other people [4]. While acute aggressive behavior occurs as a state phenomenon, the tendency to engage in aggressive behavior over the lifetime is relatively stable since childhood [5]. Most frequently, victims of violent behavior are members of patient's family; the medical personnel or other patients are on the second place [6]. It should be also noted

that often these are the first symptoms of mental illness that receive medical attention or lead to the psychiatric hospitalization.

Not surprisingly, public opinion on psychiatry is significantly influenced by the aggressive or violent behavior of psychiatric patients; community tends to over-emphasize frequency of these incidents of violent crimes. Currently there are no specific guidelines on the management of aggressive behavior in psychotic patients. The aim of our paper is to review available pharmacological interventions with special focus on the new antipsychotics. Data from published controlled trials on the efficacy of the second generation antipsychotics were critically scrutinized.

## 2. Management of agitated patient

Prediction of risk for violent behavior in psychotic patient can be a difficult task. A common accompanying factor that complicates psychotic agitation is concomitant abuse of alcohol and illicit drugs, which increases the risk of aggression [3]. Other risk factors include co-morbid personality disorders, unemployment, hyperactivity on in the clinical presentation and non-compliance with treatment; nevertheless, the best predictor of future violent behavior is a past history of violence [2, 7, 8, 9, 10]. Delusional ideas and/or commanding hallucinations may be associated with aggressive, often unpredictable behavior [2]. Although the first step should be a risk assessment, patients at the psychiatric interview are more frequently asked about violent thoughts and behavior directed to patient's themselves than about aggression to property or other persons [11]. Patient evaluation, if possible in an emergency setting, should precede any treatment initiation.

Management of agitated/aggressive patient may be difficult and perilous as it is usually provided in emergency setting, often with insufficient data on patient's history and limited possibility for proper evaluation of basic psychiatric and physical condition. Timely management and targeted treatment intervention prevents

escalation that may result in aggressive or violent behavior. The primary goal of interventions is to secure safety of the patient, staff, and other patients. The first step in the management of aggressive patients should be talking to a patient and offering help if needed. The next step is a decision to initiate oral drug treatment. In case of need, we may use assistance of other people in order to get sufficient power, outnumber agitated patient and secure physical control. If necessary, time-limited restraints or placement into seclusion may be used. Restraints should be used only when the patient poses an imminent danger to himself or others and when other less restrictive means failed [12]. Their use is temporary (2–4 hours); its application should be used to initiate treatment and to provide basic physical, instrumental and laboratory assessments. Patient in restraints usually calms down after a while [13]. Use of restraints or seclusion must be well documented, patient's mental and physical condition carefully monitored and all changes and progress of his status recorded. Seclusion or restraints are contraindicated in patients with severe physical conditions; also, drugs should be given to patients with head trauma.

Although oral treatment is preferred, options in the pharmacotherapy of acute agitation include the parenteral (intramuscular [IM], intravenous [IV]) administration of the psychotropic drugs in order to facilitate onset of drug action and quickly alleviate symptoms. So-called rapid tranquilization is the repeated administration of medication over brief time intervals, usually within an hour or half-hour period. It was recommended previously to use very high doses of haloperidol, but later studies failed to support the administration of such extreme dosing. For example, Neborsky [14] compared mean doses of 48 mg vs. 12.5 mg/day of haloperidol and Donlon [15] compared three regimens of haloperidol dose escalation (from 20 mg or 100 mg at the 5<sup>th</sup> day, 100 mg at the 10<sup>th</sup> day and stable dose of haloperidol 10 mg). In both studies, significant differences between high a lower doses of haloperidol were not found.

Treatment approaches must be comprehensive. Besides indispensable drug treatment, non-pharmacological, behavioral and environmental interventions for acute agitation are employed (*Fig. 1*). All objects near the patient that could be used as weapons (ashtrays, chairs, etc.) have to be removed, a safe passage to the secure area secured, and a sufficient number of the staff must be available. As the situation can be aggravated by overstimulation, it is helpful to screen the patient from others and turn off television and radio. We should never turn back to the agitated patient. Patients should be approached with confidence and spoken to in a soft, calm but authoritative tone. They should be allowed, asked questions designed to encourage them, to ventilate their needs. While eye contact is important, it should be broken if it makes the patient uncomfortable. The tone of the intervention is set in the first few minutes [2].

### Initial evaluation

- vital signs
- brief visual exam
- temporary diagnosis (delirium, psychosis, intoxication, etc.)

### Initial intervention

- talk to patient
- offer assistance

### Oral medication if needed and possible

### If not possible:

### Parenteral medication

### Restraints or seclusion if dangerous behavior persists

### 3. Typical antipsychotics and benzodiazepines

Pharmacological treatment is essential in control of psychotic agitation; parenteral drug administration is often needed (Table 1). Numerous factors, such as prior history and previous response to medication, play role in the choice of drug. In patients seen for the first time, somatic illness, trauma, and intoxication or withdrawal syndromes have to be ruled out [2]. Until recently, only of “typical” *antidopaminergic antipsychotics* in the form of injection were available (e.g., IM formulas of haloperidol, chlorpromazine, zuclophenthixol acetate, or levomepromazine). Dopamine D2 receptor antagonist tiapride has been used especially for the treatment of alcohol withdrawal, behavioral disturbances in the elderly and in organic mental disorders [16]. The advantages of the first generation antipsychotics include good antipsychotic efficacy, sedative effects in higher doses and several decades of experience with their administration. Their limitations are well-known adverse events including acute dystonia, extrapyramidal symptoms (EPS), akathisia, hypotension and painful injection with lower potency agents such as chlorpromazine and the risk of malignant neuroleptic syndrome. These adverse events are in contrast with the more favorable safety profiles of recently developed injection forms of second-generation antipsychotics.

*Benzodiazepines* are used in treatment of psychotic agitation for their sedative and anxiolytic effects as monotherapy or in combination with antipsychotic drugs. They can augment efficacy of the latter and subsequently reduce the dose of an antipsychotic. A recent review of controlled trials reported combination of antipsychotics and benzodiazepines to be superior

#### Advantages of typical antipsychotics (AP):

- proven antipsychotic efficacy
- sedative effect in higher dosage
- several decades of experience

#### Limitations of typical antipsychotics:

- adverse events – extrapyramidal symptoms, akathisia, (this is not a concern in acute IM treatment setting), hypotension, risk of malignant neuroleptic syndrome...
- often pharmacokinetic not evaluated
- higher rate of non-compliance
- need for drug switch if second-generation AP are subsequently chosen for long-term therapy

to the either agent alone in improvement rates and a lower incidence of EPS [17]. The most frequently prescribed are rapid acting (highly fat soluble) and/or high-potency agents such as lorazepam, clonazepam, or diazepam. The absorption of diazepam after intramuscular application is quite unpredictable, thus peroral administration is preferred. Lorazepam, the most widely used, is the only benzodiazepine that is reliably absorbed after IM administration and does not produce any active metabolite during elimination. Only a few randomized studies have found anti-aggressive effects of IM clonazepam [18], flunitrazepam [19], lorazepam [20], and midazolam [21, 22] comparable with those of haloperidol.

Benzodiazepines play a crucial role in treatment of agitation during substance withdrawal syndromes.

**Table 1:** Most common injection forms of psychotropic drugs

Drug	Dosage (mg)	Half-time (hrs)	Comments
Lorazepam	0,5–2	10–20	Can be used for treatment of alcohol withdrawal syndrome. No antipsychotic efficacy, risk of respiratory depression.
Clonazepam	1–2	20–39	Can be used for treatment of alcohol withdrawal syndrome. No antipsychotic efficacy, risk of respiratory depression.
Diazepam	5–30	50–200	Can be used for treatment of alcohol withdrawal syndrome. Long half-time, slow absorption, active metabolites.
Haloperidol	0,5–10	10–25	Risk of acute dystonia, EPS, akathisia, prolactin elevation, NMS.
Chlorpromazine	25–100	17–30	Risk of acute dystonia, EPS, akathisia, prolactin elevation, NMS.
Levomepromazine	25–50	16–78	Risk of acute dystonia, EPS, akathisia, prolactin elevation, NMS.
Zuclophenthixol	50–150	32	Risk of acute dystonia, EPS, akathisia, prolactin elevation, NMS.
Olanzapine	5–10	2–15	Risk of weight gain in long-term treatment (not in acute treatment). Low risk of EPS, does not induce prolongation of QTc interval.
Ziprasidone	10–20	4–38	Prolongation of QTc interval, low risk of EPS, does not induce weight gain.

Legend: EPS = extrapyramidal syndrome; NMS = neuroleptic malignant syndrome

The risks of respiratory depression, and dependency, tolerance and withdrawal in long-term administration, warrant caution. Benzodiazepines can augment sedative effects of other drugs and substances (alcohol), so they should not be used in patients whose medical history is not known, with unknown type of intoxication or toxicological analysis. Although rare paradoxical reactions (hostility, violence) are unlikely to militate against use in acute clinical situations, a recent French review indicates that some benzodiazepines are associated with an increased risk of aggressive behavior in special patient populations [23].

#### 4. Second generation antipsychotics

The second generation antipsychotics are generally effective and safe in the management of agitated behavior [review in: 17]. It should be noted that clozapine, the first agent of this group available for IM administration, is widely recognized as a very effective antiaggressive drug in the treatment of aggression and agitation in psychiatric patients, independent of psychiatric diagnosis [24, 25]. However, its use is limited due to the safety concerns regarding the risk of agranulocytosis. Recently, parenteral forms of two new antipsychotics have become available: ziprasidone and olanzapine; parenteral forms of other second generation antipsychotics (e.g., aripiprazole) are under development.

##### Advantages of second-generation AP in acute treatment:

- i.m. formulation, rapid dissolving tablets, wafers, and solutions available for some of the atypicals
- rapid onset of action
- rather calming than sedating effects
- better tolerability and safety in comparison with typical AP (EPS)
- more information on pharmacokinetics and dosage regimen
- continuing treatment with the same drug during acute and maintenance treatment

##### a. Olanzapine

The efficacy of olanzapine injection form has been tested in two double-blind trials of schizophrenia [26, 27], in the treatment of acutely agitated patients with mania in bipolar disorder [28], and dementia of Alzheimer or vascular types [29] (Table 2). Most study subjects required a single injection to produce therapeutic effects. The time interval needed to reach maximum plasma concentrations (15–45 min after the IM application) indicates fast onset of action. In a pharmacokinetic study in healthy subjects, a 5 mg intramuscular dose of olanzapine for injection produced on average a maxi-

imum plasma concentration which is approximately 5 times higher than the maximum plasma concentration produced by a 5 mg oral dose (company data on file). The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics is linear across the clinical dosing range. After oral administration to healthy subjects, the mean terminal elimination half-life was 33 hours and the mean olanzapine plasma clearance was 26 L/hr. Olanzapine pharmacokinetics varied on the basis of smoking status, gender, and age.

In a study of 201 patients with bipolar mania or mixed states [28], olanzapine injection (10 mg) was more effective than lorazepam (2 mg) and placebo after 2 hours in calming agitation. At the 24-hour study endpoint, olanzapine was still superior over placebo; lorazepam was not statistically different from both olanzapine and placebo. The three treatment arms showed no group difference in the frequency of adverse events.

In the first of two schizophrenia studies [27], 270 patients were randomized into six treatment groups that were given, over a period of 24 hours, one to three injections of placebo or haloperidol (7.5 mg), or one of four dosages of olanzapine (2.5 mg; 5.0 mg; 7.5 mg; 10 mg). Efficacy was assessed two hours after the first injection and adverse events after 24 hours. All active treatments were significantly better than placebo; 2.5 mg of olanzapine was less effective than the higher olanzapine doses, and haloperidol. In olanzapine treatment cells, a trend indicating better efficacy with increasing doses was observed. Moreover, the doses of 5 mg, 7.5 mg, and 10 mg showed faster onset of action: they were statistically superior to placebo already 30 minutes after administration. The most frequent adverse event was hypotension in olanzapine treated patients (seven patients, none on haloperidol or placebo). Two haloperidol treated patients developed acute dystonia, one patient on olanzapine and six on haloperidol developed treatment-emergent Parkinsonism and akathisia was observed in two olanzapine patients and three haloperidol subjects. Concomitant anticholinergic medication had to be prescribed for three haloperidol and one olanzapine treated patients.

In the second study [26], 321 patients were randomly assign to olanzapine (N=131), haloperidol (N=126), or placebo (N=54); 285 patients (91.6%) completed the study. IM olanzapine patients were administered one to three IM injections of olanzapine (10 mg) over a period of 24 hours. Evaluation at the a-priori set time points showed that olanzapine and haloperidol reduced agitation significantly better than placebo. Moreover, at assessments after 15, 30, and 45 minutes, patients receiving olanzapine displayed significantly greater improvement on the PANSS EC compared to haloperidol-treated patients, again suggesting faster onset of action. Olanzapine was also better tolerated: EPS were observed in 0.8% olanzapine treated patients compared to 5.6% patients on haloperidol. In the haloperidol group, there was a 7% incidence of acute dystonia (none in the olanzapine group). Anticholinergic medication

**Table 2:** Double-blind randomized controlled trials of olanzapine injection

Diagnosis	Study	N	Duration	Treatment arms	Results	% of responders (at 2 hrs)
Alzheimer and vascular Dementia	Meehan et al., 2002	272	24 hrs	OLZ 2.5 mg	<u>2 hrs, 24 hrs:</u>	63.4 (OLZ 2.5)
				OLZ 5.0 mg	OLZ 2.5 > PL	69.7 (OLZ 5.0)
				LOR 1.0 mg	OLZ 5.0 > PL	70.6 (LOR 1.0)
				Placebo	LOR > PL	38.8 (Placebo)
Bipolar Mania	Meehan et al., 2001	201	24 hrs	OLZ 10.0 mg	<u>2 hrs:</u>	80.6 (OLZ 10.0)
				LOR 2.0 mg	OLZ > LOR	64.7 (LOR 2.0)
				Placebo	<u>24 hrs:</u>	44.0 (Placebo)
					OLZ > PL	
					OLZ = LOR; LOR = PL	
Schizophrenia	Breier et al., 2002	270	24 hrs	OLZ 2.5 mg	<u>2 hrs:</u>	50.0 (OLZ 2.5)
				OLZ 5.0 mg	OLZ 2.5 = PL	62.6 (OLZ 5.0)
				OLZ 7.5 mg	OLZ 2.5 < OLZ 5-10, HAL	73.9 (OLZ 7.5)
				OLZ 10.0 mg	OLZ 5.0 > PL	80.4 (OLZ 10.0)
				HAL 7.5 mg	OLZ 7.5 > PL	60.0 (HAL 7.5)
				Placebo	OLZ 10.0 > PL	20.0 (Placebo)
					HAL 7.5 > PL	
Wright et al., 2001	285	24 hrs	OLZ 10.0 mg	<u>2 hrs, 24 hrs:</u>	73.3 (OLZ 10.0)	
			HAL 7.5 mg	OLZ > PL	69.0 (HAL 7.5)	
			Placebo	HAL > PL	33.3 (Placebo)	

OLZ = olanzapine; LOR = lorazepam; PL = placebo; HAL = haloperidol

had to be prescribed to 20.6% patients on haloperidol, 4.6% olanzapine patients, and 3.7% placebo subjects.

Lastly, in a double-blind trial in patients with mixed dementia [29], 272 patients were randomized to three groups: olanzapine injections (dosage 2.5 mg and 5.0 mg, respectively), were compared with injection lorazepam (1.0 mg) and placebo. Two hours after the administration both doses of olanzapine and lorazepam were more effective than placebo. This outcome was endorsed at the final 24-hour assessment: olanzapine 2.5 and 5.0 mg and lorazepam were superior over placebo according to the PANSS Excited Component Score (PANSS-EC); moreover, olanzapine 5.0 mg and lorazepam were statistically better than placebo also on the Agitation-Calmness Evaluation Scale (ACES). Important finding is a good tolerability of olanzapine injection and absence of serious adverse events in a population of elderly patients with frequent comorbidity of other medical conditions.

The rapid reduction in agitation achieved by IM olanzapine is a direct advantage to the patients. Moreover, they also benefit indirectly from the absence of the potential adverse events associated with repeated IM injections, concomitant parenteral benzodiazepines, or intravenous administration. A review of the above described double-blind studies investigated sedative and calming effects of olanzapine [30]. The ACES scale and treatment-emergent adverse events were used to assess sedation. Across all studies, 1 patient (lorazepam-treated, bipolar) became unarousable. There were no significant between-group differences in ACES scores of deep sleep or unarousability at any time across. Excluding patients who fell asleep, agitation remained sig-

nificantly more reduced with olanzapine than placebo ( $p < .05$ ). In the incidence of adverse events indicative of sedation there was no significant difference between olanzapine and the comparator drugs. For the treatment of acute agitation associated with schizophrenia, bipolar mania, or dementia, intramuscular olanzapine-treated patients did not experience more sedation than haloperidol- or lorazepam-treated patients and experienced distinct calming rather than nonspecific sedation; i.e., they became calm without sleepiness.

In a double-blind follow-up of the study of Wright and collaborators, 311 patients were switched to continuation oral treatment with olanzapine or haloperidol (both 5–20 mg/day) [31]. The results of the 4-day trial confirmed sustained efficacy during the transition from injection to tablet forms of the two drugs. Moreover, in contrast to haloperidol, olanzapine administration was not associated with severe adverse events, such as dystonia, akathisia, or other treatment-emergent adverse events.

The manufacturer of olanzapine recommends 10 mg of olanzapine injection administered as a single intramuscular injection for agitated patients with schizophrenia and bipolar mania. On the basis of individual clinical status, a second injection, 5–10 mg, may be administered as early as 2 hours after the first injection. Repeated injections should not be administered unless patients remain substantially agitated; the maximum daily dose of olanzapine of 20 mg (including all formulations) should not be exceeded. Duration of injection treatment should not be longer than 3 consecutive days.

**Table 3:** Double-blind randomized controlled trials of ziprasidone injection

Diagnosis	Study	N	Duration	Treatment arms	Results	% of responders (at 2 hrs)
Schizophrenia	Lesem et al., 2001	117	24 hrs	ZIP 2 mg	<u>1 hr, 4 hrs:</u>	57.2 (ZIP 10)
				ZIP 10 mg	ZIP 10 > PL ZIP 2	27.0 (ZIP 2)
	Daniel et al., 2001	79	24 hrs	ZIP 2 mg	<u>30 min, 4 hrs:</u>	90.2 (ZIP 20)
				ZIP 20 mg	ZIP 20 > ZIP 2	34.2 (ZIP 2)

ZIP = ziprasidone

### b. Ziprasidone

The efficacy and tolerability of ziprasidone IM in acute psychotic patients were tested in two double-blind trials [32, 33] (Table 3). Following intramuscular administration of a single dose, peak serum concentrations typically occur at approximately 60 minutes or earlier and the mean half-life ranges from two to five hours.

Parenteral ziprasidone was first compared to injectable haloperidol in a multicentric open study, in which patients were treated with injections for the first three days and subsequently switched to oral treatment up to a total duration of 7 days [34]. In a study sample of 132 psychotic patients, ziprasidone (flexible dosage 5–20 mg; maximum daily dose 80 mg) was more effective than haloperidol (2.5–10 mg, maximum 40 mg pro die) in the reduction of symptoms of agitation, had less adverse events and required fewer concomitant medications. In both double-blind studies, injection ziprasidone doses of 10 mg, respectively 20 mg were significantly superior to 2 mg of ziprasidone IM [32, 33]. In a 24-hour, double-blind, fixed-dose clinical trial of Lesem and collaborators [33], 117 acutely agitated psychotic patients were randomly assigned to receive up to 4 injections (every 2 hours p.r.n.) of 2 mg (N = 54) or 10 mg (N = 63) of ziprasidone i.m. A dose of 10 mg was significantly more effective both after 15 minutes and then at all time points from 2 hours onwards. None of the patients had significant ECG abnormalities. No acute dystonia was observed; one patient on 2 mg developed mild EPS and one patient treated with 10 mg experienced akathisia. The second trial [32] of identical design with a higher comparison dose (ziprasidone 20 mg) in a total sample of 79 patients, yielded similar results. Ziprasidone 20 mg reduced significantly agitation scores within 15 minutes following the first injection administration and did not produce any serious adverse events. Comparing onset of action, 57% of patients 10mg-treated and 90% of patients on 20 mg showed improvement 2 hours after the first injection. The authors concluded that a dose range of 10–20 mg was effective in controlling psychotic agitation, without excessive sedation; 20 mg ziprasidone was indicated for more severe symptoms.

Safe transition from parenteral to oral treatment without loss of efficacy with both ziprasidone and haloperidol has been reported for the above mentioned trials [review in: 35], and more recently in an open, randomized 7-day study of 306 patients, as well [36].

### 5. Alternative strategies

Alternative approaches to the parenteral administration of olanzapine, haloperidol, or ziprasidone include treatment with other drug formulations (risperidone solution, rapidly dissolved oral tablets of olanzapine, risperidone wafers), initiation with higher doses of antipsychotics, rapid tranquilization with the second-generation antipsychotics, or ECT.

An open-label study compared the effectiveness of risperidone liquid concentrate in treatment of acute agitation [37]. In a sample of 60 psychotic patients, the combination of risperidone (2 mg liquid concentrate) and oral lorazepam (2 mg) was as effective in controlling psychotic agitation as an intramuscular injection of haloperidol (5 mg) in combination with IM lorazepam (2 mg). Similarly, rater-blind trial of 162 acutely agitated patients with mixed diagnoses found single dose of 2 mg risperidone solution plus 2 mg of lorazepam equally effective as the combination of haloperidol injection and lorazepam [38]. In a small double-blind study were 31 agitated patients randomized to treatment with oral risperidone plus IM lorazepam, oral haloperidol plus IM lorazepam, or placebo plus IM lorazepam [39]. After 30 minutes only risperidone-treated patients showed significant improvement from baseline; at 90 minutes three treatment groups showed no difference in efficacy. Large 12-week double-blind placebo controlled study of 345 elderly patients with dementia found risperidone solution (maximum of 2 mg/day) superior to placebo in control of aggressive and agitated behavior [40].

The rapidly dissolving tablet form of olanzapine was tested in treatment of acutely ill, non-compliant patients with schizophrenia or schizoaffective disorder [41]. Rapidly dissolving olanzapine was found to be effective and safe in an open-label study of 85 psychotic patients. In addition, results indicated improved compliance during administration of rapidly dissolving tablets. A case series of 57 patients treated with high initial doses of olanzapine (up to 30 mg) over the first four hours showed efficacy and tolerability in acute agitation [42]. High initial doses could be safely reduced later on without loss of therapeutic effect. A rapid initial dose escalation approach was investigated in a double-blind study of 148 acutely agitated patients [43]. Rapid escalation of olanzapine (up to 40 mg on days 1 and 2) was compared to the usual clinical practice (initial olanzapine dose 10 mg plus lorazepam 4 mg, continuing with a dose range of olanzapine 5–20 mg daily). Results showed that rapid initial escalation dose was superior to the usual

clinical practice in reducing psychotic agitation after 24 hours and at the endpoint of the double-blind phase (day 4). Another double-blind trial with a lower dosing regime of olanzapine (initial dose 10 mg, maximum 20 mg/day within 3 days) also confirmed effectiveness of rapid dose escalation in control of agitation in schizophrenia [44].

ECT in combination with antipsychotic medication may be considered for patients with schizophrenia or schizoaffective disorder who have severe psychotic symptoms that have not responded to treatment with an antipsychotic medication. More recent reports suggest that better therapeutic benefit may be seen with combined use of ECT and second generation antipsychotic medication [45]. This may be true for aggressive behavior in schizophrenia, as well [46]. Besides schizophrenia patients, results of open trials and case series indicating good efficacy of ECT in the control of agitation associated with bipolar mania [47, 48], and dementia [49, 50] has also been published.

## 6. Other psychotropic drugs and treatment of persistent agitation

Data on the anti-aggressive effects of other psychotropic drugs are limited; more evidence about the scope and mechanism of their action is needed to subsequently identify their role in the clinical practice. For example, wide-spread use of mood stabilizers for the control of behavioral disturbances in various psychiatric disorders, mostly based on the empirical experience, has been just recently supported by controlled studies. In addition to the anecdotal reports on the intravenous administration of valproate for acute agitation [51, 52], add-on oral valproate [e.g., 53, 54, 55; review in 56], carbamazepine [e.g., 57, 58, 59], or topiramate [60] showed calming effects. Lithium, a standard treatment of agitation in bipolar mania, possesses reliable anti-aggressive efficacy, as well [e.g., 61, 62, 63, 64, 65]. Promising findings from numerous trials indicate the anti-aggressive effects of selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, sertraline) as add-on medication [e.g., 66; review in 67]. Evidence of the anti-aggressive efficacy of beta-blockers derives mostly from the treatment of patients with organic disorders [68, 69, 70, 71]. Clinical usefulness of the alpha-2 receptor antagonist drug clonidine in the treatment of aggression has been tested in a few trials of aggressive children with irritable autistic and conduct disorder [72, 73].

In the long-term treatment of persistent psychotic agitation [review in 2], second generation antipsychotics are the most used common treatment option. Clozapine's efficacy is proven and there are again empirical data supporting the use of mood stabilizers (valproate, carbamazepine, lithium) [74]. Electroconvulsive therapy remains a non-pharmacological treatment option for drug-refractory persistent agitation.

## 7. Conclusions

There is a growing number of publications indicating that second generation antipsychotics are the agents of choice for the treatment of psychotic disorders; the same pattern can be observed in drug therapy of psychotic agitation. Parenteral forms of new antipsychotics are effective and safe in the control of acute agitation in psychotic patients. Evidence-based alternative approaches to injection forms (olanzapine, ziprasidone) are the liquid forms (risperidone), orally dissolving tablets (olanzapine, risperidone), treatment with high initial doses of drug, or rapid dose escalation (olanzapine).

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