



THE PHARMACOLOGICAL APPROACH IN THE MANAGEMENT OF PSYCHOMOTOR AGITATION — EXPERIENCE FROM CROATIAN PSYCHIATRISTS

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SUMMARY – Psychomotor agitation is a state of motor restlessness and intrapsychic tension that requires fast recognition and adequate assessment and management to minimize patient anxiety and reduce the risk for escalation to aggression and violence. It may be caused by a variety of psychiatric conditions (psychotic disorders, intellectual disability, autism, affective and anxiety disorders, personality disorders), substance abuse and/or intoxication or withdrawal and a wide range of general medical conditions. Numerous factors influence the final decision on the choice of adequate pharmacotherapy, such as clinical presentation, compliance, age, sex, comorbidities and the availability of certain drugs that are indicated in the management of psychomotor agitation.

Since clinical practice is frequently based on medications or their combinations, as well as the routes of administration that are not supported by existing evidence coming from research, we conducted a multi-centric investigation in which we included Croatian psychiatrists working in acute wards, since they are the ones caring for the majority of patients presenting with agitation. For this purpose, we created a questionnaire consisting of 13 questions related to the pharmacological treatment of agitation in terms of the most commonly used medications, their route of administration, combinations and adverse effects. The results of this research will serve as a basis for the development of a Croatian protocol for the pharmacological treatment of patients presenting with severe agitation.

Keywords: *agitation; aggression; antipsychotics*

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Introduction

Psychomotor agitation is a frequent phenomenon in patients with psychiatric disorders representing a clinically important issue not only in emergency settings or inpatient units, but also in outpatient care or any other clinical field dealing with this type of patients. It is best defined as a state of restlessness combined with excessive motor activity and irritability that requires immediate attention, and adequate assessment and management to minimize the patient's anxiety and risk of escalation to aggression and violent behavior. Other definitions include more detailed descriptions of excessive motor activity that mainly consists of various non-productive and repetitious behaviors, such as pacing, fidgeting and the inability to sit still¹. Agitation is associated with a variety of psychiatric conditions, including psychotic disorders, affective and anxiety disorders, personality disorders (mostly antisocial and borderline personality disorder) and autism, as well as substance abuse and/or intoxication or withdrawal². Agitation can also be a leading symptom of several central nervous system diseases, such as Alzheimer's disease or any other type of dementia, encephalitis or meningitis, as well as some general medical conditions, such as thyrotoxicosis or delirium^{3,4}. Psychomotor agitation has also been described as a possible predictor of suicidal behavior in patients with depression, as well as an indicator for the presence of underlying bipolar disorder in those patients¹.

Given the omnipresence of agitation in psychiatric conditions, as well as in many general medical conditions, it is essential to understand its possible causes and promptly manage this behavior, as it is crucial to gain control over it to prevent a possible escalation into aggression and violence. There are several available guidelines for the assessment and management of agitation that focus on the use of different pharmacological interventions combining various pharmacological agents. The American Association for Emergency Psychiatry with its Project BETA discourages the use of medication as a restraint and encourages non-pharmacological approaches such as verbal de-escalation. If medication becomes necessary, using multiple medications is not recommended due to a higher risk of over-sedation and interactions between different medications⁵. In addition, oral formulations are preferred over intramuscular ones if the patient is able

to cooperate. For the treatment of psychosis-related agitation in patients with a known psychiatric disorder, antipsychotics are preferred over benzodiazepines because they directly address the cause of agitation in these patients. Second-generation antipsychotics (risperidone 2 mg, olanzapine 5-10 mg) administered orally are recommended over oral haloperidol either alone or with an adjunctive medication, mostly benzodiazepines (lorazepam 1-2 mg). If the patient cannot cooperate with oral medications, intramuscular ziprasidone or olanzapine is recommended⁵.

If the underlying cause of agitation is not known, a benzodiazepine is recommended as first-line treatment. Despite second-generation antipsychotics (SGA) being recommended over the first generation (FGA) ones, there is no real evidence pointing to SGA being more effective in treating agitation than FGA. Controlled trials show oral olanzapine and aripiprazole to be the most effective, having the same effectiveness as haloperidol¹.

Regarding FGA, studies show the combination of haloperidol and levomepromazine was superior to oral haloperidol mono-therapy. Moreover, haloperidol in combination with benzodiazepines was as efficacious as olanzapine and better than haloperidol alone.

According to rapid tranquillization guidelines (NICE, UK), which refer to the use of parenteral medication (intramuscular, exceptionally intravenous) in cases where oral administration is not an option, intramuscular lorazepam alone or, if there is no response, haloperidol in combination with intramuscular promethazine is recommended⁶.

In general, the pharmacological treatment of agitation should result in calming patients without over-sedating them. Oral or inhalation formulations are preferred over intramuscular ones, while intravenous formulations should be avoided altogether, if possible. The guidelines on treating agitation are still not completely clear or unique, which is why they require more attention and thorough research.

In 2016, the Croatian Psychiatric Society published guidelines for the prevention of aggressive behavior and use of measures of restraint in psychiatry titled "Strategies for the prevention of aggressive behavior", which includes de-escalation techniques, the use of restraint and seclusion, but not pharmacological intervention or rapid tranquillization.

Therefore, Croatian guidelines on psychomotor agitation treatment are sparse and do not follow evidence from controlled clinical trials.

The aim of this study was to investigate the most frequently administered medications or their combinations by psychiatrists working in acute wards in Croatia to help the development of a Croatian protocol for the pharmacological treatment of patients presenting with severe agitation.

Methods

We conducted a multi-centric investigation between May and August 2018 that included Croatian psychiatrists working in acute wards, since they are the ones that care for the majority of psychiatric patients presenting with severe agitation. For this purpose, we created a questionnaire consisting of 13 questions related to the pharmacological treatment of agitation in terms of the most commonly used drugs, their route of administration, their combinations and most commonly occurring adverse effects.

Results

Of the 531 psychiatrists currently practicing in Croatia, 77 participated in this study and they are employed in the following institutions: University Hospital Centre Zagreb, Sestre milosrdnice University Hospital Center, General Hospital Varaždin, University Hospital Centre Rijeka, University Psychiatric Hospital Vrapče, Neuropsychiatric Hospital “Dr. Ivan Barbot” Popovača, University Hospital Centre Split, University Hospital Centre Osijek, General Hospital Koprivnica and General Hospital Vinkovci. The questionnaire consisted of 13 questions, each question with several response options. The questionnaire is shown in Table 1 along with the answers given by the surveyed psychiatrists.

The majority of the surveyed psychiatrists, 76 (98.7%) of them, reported haloperidol as the drug of choice for an agitated, psychotic and uncooperative patient, and most of them, 73 (94.8%), preferred parenteral administration. A total of 50 (64.9%) psychiatrists reported giving a combination of antipsychotics

and benzodiazepines to the majority of agitated patients, and for 68 (88.3%) the combination of choice was haloperidol, promazine and diazepam. For those who reported using the combination of haloperidol, promazine and diazepam, the preferred dose of haloperidol was 5 mg for 43 (55.8%) psychiatrists and 68 (88.3%) preferred intramuscular administration. For promazine, the preferred dose was 100 mg for 39 (50.6%) respondents and 72 (93.5%) tended to use it intramuscularly, whereas for diazepam the majority, 41 (53.2%) reported using both the intravenous and intramuscular route, depending on the clinical presentation. Most of the surveyed psychiatrists, 35 (45.4%), reported their patients respond to the given medication (the combination of haloperidol, promazine and diazepam) 30 minutes after administration. The most commonly reported side effect after the combination in question is sedation, according to 69 (89.6%) of the surveyed psychiatrists and moreover, 62 (80.5%) psychiatrists reported having no increase in the incidence of malignant neuroleptic syndrome after using haloperidol, promazine and diazepam. Lastly, 72 (93.5%) respondents reported they never had a patient suddenly die after being given the combination of haloperidol, promazine and diazepam.

Discussion

Our research showed that Croatian psychiatrists prefer haloperidol for the treatment of acute agitation. This medication has been proven effective and studies have shown it to be even more effective if used in combination with benzodiazepines^{1,7}, which is what the majority of the surveyed Croatian psychiatrists tend to do — combine haloperidol with diazepam. The preferred combination of medications used by Croatian psychiatrists seems to be haloperidol, promazine and diazepam. Evidence from clinical trials has not reported any more side effects from this combination in comparison to any other combination of medications. In addition to helping minimize extrapyramidal side effects from haloperidol, benzodiazepine adds more sedation, which helps eliminate agitation more effectively and in a timely manner due to having a fast onset of action, especially diazepam (15 minutes). Researches have suggested using mono-therapy over

Table 1. Medication Choices and Administration Practices for Managing Severely Agitated, Psychotic, and Uncooperative Patients

Question	Answer	N	(%)
1. What is your medication of choice for a severely agitated, psychotic and uncooperative patient (you can choose multiple answers)?	Haloperidol	76	98.7
	Zuclopenthixol	4	5.2
	Olanzapine	9	11.7
	Risperidone	0	0
	Promazine	43	55.8
	Ziprasidone	1	1.3
	Diazepam	47	61
2. What is the route of administration you prefer?	Oral	4	5.2
	Parenteral	73	94.8
3. How do you administer the medication?	Monotherapy, always	1	1.3
	Occasionally, adding diazepam or another benzodiazepine with the antipsychotic	26	33.8
	Usually as politherapy; combining antipsychotics with benzodiazepines	50	64.9
4. Do you ever use the combination of haloperidol, promazine and diazepam for the treatment of severe agitation?	Yes	32	41.5
	No	9	11.7
	Occasionally	28	36.4
	Often	8	10.4
5. If you do use the combination of haloperidol, promazine and diazepam, what is your preferred dose of haloperidol?	5mg	43	55.8
	10mg	33	42.8
	Other (up to 15mg)	1	1.3
6. If you do use the combination of haloperidol, promazine and diazepam, what is your preferred dose of promazine?	50mg	37	48
	100mg	39	50.6
	Other (3x50mg up to 3x100mg)	1	1.3
7. What is your preferred parenteral route of administration for haloperidol?	Intramuscular	68	88.3
	Intravenous	0	0
	Both, depending on the patient	9	11.7
8. What is your preferred parenteral route of administration for promazine?	Intramuscular	72	93.5
	Intravenous	0	0
	Both, depending on the patient	5	6.5
9. What is your preferred parenteral route of administration for diazepam?	Intramuscular	34	44.1
	Intravenous	0	0
	Both, depending on the patient	41	53.2
10. How long after administering the combination of haloperidol, promazine and diazepam is clinical improvement noticed?	After 15 minutes	19	24.7
	After 30 minutes	35	45.4
	After 45 minutes	17	22
	After 60 minutes	6	7.8
	After 90 minutes	4	5.2
	After 120 minutes	2	2.6

Table 1. [Continued]

Question	Answer	N	(%)
11. What is the side effect you noticed occurring most frequently after using the combination of haloperidol, promazine and diazepam?	Sedation	69	89.6
	Acute extrapyramidal side effects	11	14.3
	Hypotension	34	44.1
	Bradycardia	0	0
	Respiratory failure	1	1.3
	Headache	0	0
12. Did you notice an increase in the incidence of malignant neuroleptic syndrome after using the combination of haloperidol, promazine and diazepam?	Yes	0	0
	No	62	80.5
	Rarely	12	15.6
	Often	0	0
	Unanswered	3	3.9
13. Did you ever have sudden death occur after administering the combination of haloperidol, promazine and diazepam?	Once	2	2.6
	Twice	0	0
	Three times	0	0
	More than 3 times	0	0
	Never	72	93.5
	Unanswered	0	0

polytherapy to avoid major side effects, but in this research, Croatian psychiatrists reported having no increase in the incidence of more severe side effects — the main side effect was sedation — while extrapyramidal side effects were rare. An important possible idiosyncratic reaction to this type of polytherapy is malignant neuroleptic syndrome (MNS) and Croatian psychiatrists reported no increase in its incidence when using haloperidol, promazine and diazepam together. This finding is contradictory to research performed so far and proves that in Croatian clinical practice the combination of these medications is effective and safe for most patients presenting with severe agitation. Although polytherapy involving high-potency FGAs can be one possible risk factor for the development of MNS, it is not the only one⁸. Other important risk factors include young age, male sex and genetic predisposition^{9,10}. Additional risk factors like preexisting organic pathologies of the central nervous system, lithium treatment, infection/exsiccosis and withdrawal from medication with anticholinergic properties or alcohol could also be important in the development

of MNS⁸. The development of MNS may include the synergistic effect of several or all of the mentioned risk factors, which can serve as an explanation for the low incidence of this life-threatening side effect occurring from polytherapy including the combination of haloperidol promazine and diazepam demonstrated in this study. Another possibility for the low incidence of MNS is the fact that serious psychomotor agitation is not that common, so the combination of haloperidol, promazine and diazepam is not needed as often.

When clonazepam, a benzodiazepine, was compared to haloperidol in the treatment of agitation, both produced a significant reduction of agitation within 2 hours of initial treatment, but haloperidol showed a more rapid onset of action, which is preferred when treating agitation, since it progresses rapidly into aggression and violence. The combination of haloperidol, promazine and diazepam is once again suitable, since both haloperidol and diazepam have a fast onset of action (within 15 minutes for diazepam and 20-30 minutes for haloperidol). Most of the surveyed Croatian psychiatrists reported the onset of action of the

combination of haloperidol, promazine and diazepam to be around 30 minutes.

Mantovani *et al.* showed haloperidol in combination with promethazine to be more effective and have a faster onset of action than haloperidol alone¹¹. Promethazine is a phenothiazine neuroleptic and a strong H1 antagonist. Promazine, which tends to be used in Croatia, is also a drug from the phenothiazine group and is an FGA known to be among the most potent H1 antagonist antipsychotics. Haloperidol has no affinity for H1 receptors, which makes combining it with promazine, as it is done in Croatian psychiatric practice, justified and in line with evidence from clinical studies. In addition, a study by Higashima *et al.* demonstrated the combination of oral haloperidol with levomepromazine to be superior to oral haloperidol mono-therapy in treating agitation¹². The combination of haloperidol, promazine and diazepam covers a broad spectrum of receptors, allowing for tranquillization to be as effective and timely as possible.

Even though oral formulations are preferred over intramuscular ones, being a less aggressive way of administering medications, in emergency psychiatry settings, intramuscular or even intravenous formulations are irreplaceable in treating severely agitated and uncooperative patients¹³. This was confirmed by Croatian psychiatrists that participated in this study, as well.

If we compare the most commonly used combination of medications in Croatian clinical practice to the NICE, UK rapid tranquillization guidelines, there are similarities in terms of the types of medications used. The Guidelines recommend using intramuscular lorazepam as initial therapy for agitation and, in cases where there is no response to lorazepam, adding intramuscular haloperidol combined with intramuscular promethazine. This combination is similar to the combination used in Croatia, the only difference is that, instead of lorazepam, Croatian psychiatrists use another benzodiazepine — diazepam — and instead of promethazine they use promazine, both from the phenothiazine group of neuroleptics that have an effect on the same receptor groups. The reason behind using diazepam and promazine instead of lorazepam and promethazine is that parenteral lorazepam and promethazine are not available in Croatia.

The results of different studies suggest that a combination of different medications used to treat

agitation presents a higher risk of over-sedation and a higher possibility of unwanted interactions between different medications⁵. It is important to note that research is still really sparse, since it is hard or almost impossible to get an agitated patient to consent to a clinical trial. An important emphasis from the existing recommendations is to try to determine the most likely cause of agitation in a patient, which helps determine a course of action if agitation is caused by a non-psychiatric medical condition or delirium⁵. Also, it is recommended to use haloperidol in combination with benzodiazepines to reduce extrapyramidal side effects, instead of using haloperidol as mono-therapy.

However, even though official guidelines published by different international expert groups and associations may be of help when deciding on which medication is appropriate for treating agitation, they are not in any way binding. The most important goal is to achieve a fast decrease of agitation in a patient with any medication or combination of medications that have proven to be the most effective and safe in clinical practice. In the case of Croatian psychiatrists, the most effective combination is haloperidol, promazine and diazepam and it is the one most commonly used by Croatian psychiatrists working in acute wards. According to this research, the combination of haloperidol, promazine and diazepam is not only effective, but also safe for the patients despite having great potential for the development of side effects, either from over-sedation or interactions between medications. This is why additional research is necessary to confirm or refute the use of haloperidol, promazine and diazepam together as the first choice for rapid tranquillization.

Conclusion

One of the main issues regarding the treatment of severe agitation is a lack of consistency in different recommendations in terms of which medications and combinations of medications to use; a fact which is necessary even though clinical studies showed most of the recommended medications to be similarly effective. Our questionnaire helped determine which medication is most commonly used in clinical practice in Croatia and how effective it is. According to the questionnaire, most psychiatrists seem to use the same

combination of medications in similar doses without reporting an increase in the incidence of major side effects or sudden deaths, which makes it a justified line of therapy, when clinically indicated.

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Sažetak

FARMAKOLOŠKI PRISTUP ZBRINJAVANJU PSIHOMOTORNE
AGITACIJE – ISKUSTVA HRVATSKIH PSIHIJATARA

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Psihomotorna agitacija je stanje motoričkog nemira i intrapsihičke napetosti koje zahtijeva brzo prepoznavanje, adekvatnu procjenu i odgovarajuće postupanje kako bi se smanjila tjeskoba pacijenta i spriječila eskalacija prema agresiji ili nasilju. Ovo stanje može biti uzrokovano različitim psihijatrijskim poremećajima (psihotični poremećaji, intelektualne teškoće, poremećaji iz spektra autizma, afektivni i anksiozni poremećaji, poremećaji ličnosti), zluporabom psihoaktivnih tvari i/ili intoksikacijom ili sindromom ustezanja, kao i širokim spektrom somatskih bolesti. Na konačan izbor odgovarajuće farmakoterapije utječe niz čimbenika, poput kliničke slike, suradljivosti pacijenta, dobi, spola, komorbiditeta te dostupnosti pojedinih lijekova koji se primjenjuju u liječenju psihomotorne agitacije. Budući da se u kliničkoj praksi često primjenjuju lijekovi, njihove kombinacije i načini primjene koji nisu uvijek utemeljeni na dostupnim znanstvenim dokazima, proveli smo multicentrično istraživanje u kojem su sudjelovali hrvatski psihijatri zaposleni na akutnim odjelima jer upravo oni najčešće skrbe o pacijentima koji dolaze s izraženom agitacijom. U tu svrhu izrađen je upitnik s 13 pitanja, koja obuhvaćaju teme vezane uz farmakološko liječenje agitacije, prvenstveno najčešće korištene lijekove, njihove načine primjene, kombinacije lijekova te nuspojave. Rezultati ovog istraživanja poslužit će kao temelj za izradu hrvatskog protokola za farmakološko liječenje pacijenata s izraženom agitacijom.

Ključne riječi: *agitacija; agresija; antipsihotici*