Psychopharmacology (2020) 237:3497–3501
https://doi.org/10.1007/s00213-020-05644-3

LETTER TO THE EDITOR

Psychomotor agitation and hyperactive delirium in COVID-19 patients treated with aripiprazole 9.75 mg/1.3 ml immediate release

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Received: 29 May 2020 / Accepted: 17 August 2020 / Published online: 21 August 2020

Delirium and psychomotor agitation are relevant clinical conditions that may develop during COVID-19 infection, especially in intensive care unit (ICU) settings, in patients with acute respiratory distress and in isolation environments (Qiu et al. 2020). Delirium is characterized by a state of acute confusion presenting with a change in mental status, associated with altered level of consciousness, impaired attention and concentration, and disorganized thinking (American Psychiatric Association 2013). Hallucinations, illusions, or delusions may also occur. For a number of patients, delirium is reversible within a period of days. However, for other patients, it may progress to permanent brain failure. Florid delirium with intense agitation in a combative patient is often described as hyperactive delirium, whereas the clinical picture in which delirium presents in a calm and quiet patient is often referred to as hypoactive delirium.

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Both hyperactive and hypoactive delirium subtypes may be among the presenting symptom of the underlying infectious disease, particularly in the elderly in the ICU (Marcantonio 2018). Delirium may also develop during the course of COVID-19 infection, significantly complicating disease management. As for several other respiratory viruses, accruing evidence indicates that human coronaviruses (HCoVs) are not always confined to the upper respiratory tract but have neuroinvasive properties (Desforges et al. 2020) and are potentially associated with short- and long-term neurological sequelae, including an acute encephalopathy that manifests clinically with delirium (Algahtani et al. 2016). The development of delirium follows a stress-vulnerability model with precipitating factors that include severe infection, acute respiratory distress, invasive ventilation in ICU settings, and old age (Quinlan et al. 2011). These potential risk factors characterize the epidemiology and clinical spectrum of the current COVID-19 outbreak in Italy. Furthermore, medications used as first-line treatment in COVID-19 patients, like antiretroviral, can cause or contribute to delirium (Ely et al. 2004). Moreover, psychiatric patients are at a greater risk of infection and their psychopathological proneness may increase the likelihood of psychomotor agitation, even in patients with mild symptoms (Yao et al. 2020).

Medication treatment of delirium needs to be weighed against the risk of side effects. Where non-pharmacological measures are unsuccessful or rapid control is required, it may be necessary to provide a pharmacological management earlier than would routinely be considered. The high transmission rate of COVID-19 and the resulting risk of harm to others may exceed risk of harm to the individual, further prompting earlier use of pharmacological treatments for potentially risky behaviors. In this context, the NICE guidelines on violence and aggression may help clinical management (National Institute for Health and Care Excellence 2015). Pharmacological interventions must also take into account the specific clinical

Table 1 Clinical characteristics, physical and psychiatric comorbidities, improvements in delirium/psychomotor agitation, adverse effect, and final outcome of 16 Caucasian patients with COVID-19 infection. Day: number of days with active COVID-19 symptoms; Δ ICDS and Δ MOAS: score differences between baseline and after 2 h from the administration of aripiprazole 7.5 mg i.m. at the Intensive Care Delirium Screening Checklist and at the Modified Overt Aggression Scale; final outcome: it refers to the COVID-19 infection

N	Age	Sex	Clinical condition	Day	Physical comorbidities	Psychological comorbidities	Current therapy	Critical episode	Pre-dose ICDSC	Post-dose ICDSC	Pre-dose MOAS	Post-dose MOAS	Adverse effects	Final Outcome
1	77	M	Interstitial pneumonia in non-invasive mechanical ventilation	7	Prostatic hypertrophy	None	Hydroxychloroquine (800 mg/day), ritonavir (100 mg/day), valaciclovir (3000 mg/day), darunavir (800 mg/day), cardioaspirin (100 mg/day)	Delirium (hyperactive), paranoid ideation	6	1	28	11	Mild sedation	Recovered
2	61	M	Interstitial pneumonia in non-invasive mechanical ventilation	5	Hypertension	Major depression	Hydroxychloroquine (400 mg/day), morphine (10 mg/ml/i.m.), enoxaparin (4000 UI/day), methylprednisolone (40 mg/ml/day), alprazolam (2 mg/day), pregabalin (75 mg/day)	Delirium (hyperactive)	6	2	26	18	None	Currently in treatment
3	60	M	Mild symptoms (fever, ageusia, asthenia)	15	Dyslipidemia	Major depression with psychotic features	Hydroxychloroquine (400 mg/day), ceftriaxone (2 g/day), azitromicyn (500 mg/day), enoxaparin (4000 UI/day), sertraline (50 mg/day), delorazepam (4 mg/day)	Delirium (hyperactive), delusion of guilt, suicide ideation	4	2	20	9	None	Currently in treatment
4	58	M	Interstitial pneumonia in invasive mechanical ventilation	5	Hypertension, vocal cord polyposis	Bipolar disorder	Hydroxychloroquine (800 mg/day), ceftaroline (1.2 g/iv/day), meropenem (3 g/day), aripiprazole (15 mg/day)	Delirium (hyperactive)	5	2	24	8	None	Recovered
5	75	M	Interstitial pneumonia in non-invasive mechanical ventilation	4	Hypertension	None	Hydroxychloroquine (400 mg/day), Norvir (100 mg/day), oseltamivir (30 mg/day), ceftaroline (600 mg/day), tamusolin (0.4 mg/day), Prezista (800 mg/day)	Delirium (hyperactive)	6	2	27	19	Mild sedation	Recovered
6	72	M	Interstitial pneumonia in non-invasive mechanical ventilation	2	Ventricular fibrillation, bacteremia due to hip replacement	None	Hydroxychloroquine (800 mg/day), darunavir (800 mg/day), ritonavir (100 mg/day), oseltamivir (150 mg/day), ceftaroline (1800 mg/day), warfarin (5 mg/day), amiodarone (200 mg/day)	Delirium (hyperactive)	5	1	23	5	None	Recovered
7	47	M	Interstitial pneumonia in invasive mechanical ventilation	6	None	None	Hydroxychloroquine (200 mg/day), Norvir (100 mg/day), oseltamivir (75 mg/day), ceftaroline (600 mg/day), tamusolin (0.4 mg/day), Prezista (800 mg/day), aripiprazole (15 mg/day)	Delirium (hyperactive)	5	2	27	10	None	Currently in treatment
8	53	M	Interstitial pneumonia in non-invasive mechanical ventilation	12	Hypertension	None	Hydroxychloroquine (400 mg/day), dexamethasone (20 mg/day), darunavir (800 mg/day), ritonavir (100 mg/day), omeprazole (20 mg/day), olmesartan (10 mg/day)	Delirium (hyperactive)	5	1	21	11	None	Currently in treatment

Table 1 (continued)

N	Age	Sex	Clinical condition	Day	Physical comorbidities	Psychological comorbidities	Current therapy	Critical episode	Pre-dose ICDSC	Post-dose ICDSC	Pre-dose MOAS	Post-dose MOAS	Adverse effects	Final Outcome
9	55	M	Interstitial pneumonia in non-invasive mechanical ventilation	8	Hypertension	None	Hydroxychloroquine (400mg/day), dexamethasone (20 mg/day), darunavir/cobicistat (800/150 mg/-day), atenolol (50 mg/day)	Delirium (hyperactive), aggressive behavior	5	2	24	14	Mild sedation	Currently in treatment
10	64	M	Interstitial pneumonia in non-invasive mechanical ventilation	6	Hypertension, dyslipidemia, obesity	Depressive disorder	Hydroxychloroquine (400 mg/day), lopinavir/ritonavir (800/200 mg/day), tocilizumab (560 mg/day), cardioaspirin (100 mg/day), rosuvastatin (20 mg/day), losartan (50 mg/day), citalopram (20 mg/day) lorazepam (2 mg/day)	Delirium (hyperactive)	5	2	21	16	None	Currently in treatment
11	67	M	Interstitial pneumonia in non-invasive mechanical ventilation	15	Hypertension	Bipolar disorder	Hydroxychloroquine (200 mg/day)	Delirium (hyperactive)	5	2	23	13	None	Currently in treatment
12	61	M	Interstitial pneumonia in non-invasive mechanical ventilation	11	Hypertension, dyslipidemia	None	Tocilizumab (560 mg/day), enoxaparin (4000 UI/day), methylprednisolone (40 mg/ml/day)	Delirium (hyperactive)	8	1	31	26	None	Currently in treatment
13	72	M	Interstitial pneumonia in non-invasive mechanical ventilation	9	Recent cholecystectomy	None	Hydroxychloroquine (200 mg/day), Norvir (100 mg/day), oseltamivir (30 mg/day)	Delirium (hyperactive)	6	0	26	9	None	Currently in treatment
14	90	M	Interstitial pneumonia in non-invasive mechanical ventilation	4	Mitral/aortic valve incompetence, chronic renal failure	None	Linezolid 1200 mg/day, methylprednisolone (20 mg/ml/day), Clexane 400 mg/day, morphine 5 mg/day	Delirium (hyperactive)	5	2	25	9	Mild sedation	Death
15	71	M	Interstitial pneumonia in non-invasive mechanical ventilation	2	Recent coronary bypass, history of cardiac ischemia	Generalized anxiety disorder	Sulfamethoxazole + trimethoprim (400 mg/5 ml + 80 mg/5 ml continuous infusion), cardioaspirin (100 mg/day), enoxaparin (4000 UI/day)	Delirium (hyperactive), persecutory ideation	6	0	32	5	Mild sedation	Recovered
16	86	M	Interstitial pneumonia in non-invasive mechanical ventilation	18	None	None	Haloperidol (0.5 mg/day), nystatin (100.000 UI/day), KCl (600 mg/day), Clexane 400 mg/day, ceftriaxone (2 g/day)	Delirium (hyperactive)	4	1	23	7	None	Currently in treatment

features of COVID-19 infections, namely the high risk of respiratory depression and the possible pharmacokinetic interactions with antiviral agents, especially in the elderly (Schoen et al. 2013). Available injectable medications for delirium and psychomotor agitation include (1) dexmedetomidine, an alpha 2 agonist with sedative and anxiolytic properties that is associated with a low risk of inducing respiratory depression but possible pharmacokinetic interactions with antiviral agents as well as hypotension, hypertension, and bradycardia; (2) haloperidol, often used for hyperactive delirium, associated with QTc prolongation, arrhythmias, and extrapyramidal symptoms; (3) promazine and (4) tiapride that may be both associated with increased risk of arrhythmias and respiratory depression; (5) olanzapine, a second-generation antipsychotic; and (6) aripiprazole, a third-generation antipsychotic agent with a dopamine receptor–binding profile distinct from other antipsychotics. Small non-inferiority trials have shown that these agents are equally effective in delirium and choice is based on adverse effects, although a recent study proposed aripiprazole as the potential drug of choice for the management of delirium (Prommer 2017).

We hereby describe the case of 16 consecutive patients with COVID-19 whose hyperactive delirium (psychomotor agitation with restlessness and/or aggressiveness, hyper-vigilance, and hallucinations/delusion) was treated with aripiprazole 9.75-mg/1.3-ml intramuscular injections in the hospitals of Bergamo, Brescia, Genoa, Ancona, and Chieti, inside the Italian "red area," at the beginning of the epidemic phase (Table 1). Of these patients, 11 were admitted in an ICU. Aripiprazole was chosen in light of its pharmacodynamic and pharmacokinetic properties (low antihistaminic effects, absence of anticholinergic effects, low risk of interaction (Liverpool Drug Interaction Group 2020) with antiviral agents and chloroquine/hydroxychloroquine), and relatively favorable adverse effect profile (low risk of arrhythmias, low risk of respiratory depression), and in accordance with recommendations recently issued from the Italian Society of Epidemiology and Psychiatry (Ostuzzi et al. 2020).

Aripiprazole injection rapidly and significantly reduced signs and symptoms of delirium and psychomotor agitation, as measured by using the Intensive Care Delirium Screening Checklist (ICDS) ($t = 1.86$; $p < 0.05$) and the Modified Overt Aggression Scale (MOAS) ($t = 8.95$; $p < 0.001$). Tolerability was high, and no severe adverse events were observed, even in severely ill patients in ICU settings, in treatment with antiviral drugs, antimalarial agents (hydroxychloroquine), and immunosuppressive drug (tocilizumab). From a pharmacokinetic point of view, the elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4 (Boulton et al. 2008). Intramuscular aripiprazole demonstrated more rapid attainment of plasma aripiprazole concentrations than oral aripiprazole, being able to determine a faster clinical response in terms of efficacy (Boulton et al. 2008).

Bearing in mind that there are no FDA medications that are specifically indicated for the treatment of delirium (for instance, aripiprazole injection is indicated for agitation associated with schizophrenia or bipolar mania), the present case series provides preliminary evidence on the safety and effectiveness of injectable aripiprazole use for patients with COVID-19, delirium, and/or psychomotor agitation. These data could be of interest for those psychiatrists that will face the development of delirium/psychomotor agitation in COVID-19 patients requiring rapid and prompt treatment, when the presence of physical comorbidities and concomitant medications can complicate the choice of the right pharmacological intervention. Future data from RCTs are requested to confirm and further develop this pharmacological intervention.

Acknowledgments In memory of all Italian medical doctors who died for COVID-19.

Compliance with ethical standards

Conflict of interest Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen, Lundbeck, Otsuka, and Pfizer. Stefano Barlati has been a speaker for Angelini, Janssen, Lundbeck, and Otsuka. Mario Amore has been a speaker for GSK. Alessandro Cuomo has been a consultant and/or a speaker for Angelini, Lundbeck, and Otsuka. Andrea Fagiolini has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boheringer Ingelheim, Daiichi Sankyo Brasil Farmacêutica, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, and Vifor. Massimo di Giannantonio has been a consultant and/or a speaker and/or has received research grants from Angelini, Janssen, Lundbeck, Otsuka, Pfizer, and Recordati.

References

Algahtani H, Subahi A, Shirah B (2016) Neurological Complications of Middle East Respiratory Syndrome Coronavirus: A Report of Two Cases and Review of the Literature. Case Rep Neurol Med; 3502683

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Arlington

Boulton DW, Kollia G, Mallikaarjun S, Komoroski B, Sharma A, Kovalick LJ, Reeves RA (2008) Pharmacokinetics and tolerability of intramuscular, oral and intravenous aripiprazole in healthy subjects and in patients with schizophrenia. Clin Pharmacokinet 47(7): 475–485

Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, Talbot PJ (2020) Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses **12**:14

Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA **291**:1753–1762

Liverpool Drug Interaction Group (2020) Drug-drug interactions and COVID-19. http://www.covid19-druginteractions.org

Marcantonio ER (2018) Delirium in Hospitalized Older Adults. N Engl J Med 378(1):96–97

National Institute for Health and Care Excellence. (Violence and aggression: short-term management in mental health, health and community settings. 2015). Available at: https://www.nice.org.uk/guidance/ng10/resources/violence-and-aggression-shortterm-management-in-mental-health-health-and-community-settings-pdf-1837264712389 [Accessed 17 March 2020]

Ostuzzi G, Amaddeo F, Michencigh G, Fagiolini A, Imperadore G, Barbui C (2020) https://siep.it/psicofarmaci-e-covid-19/

Prommer E (2017) Aripiprazole: A New Option in Delirium. Am J Hosp Palliat Care **34**:180–185

Qiu HB, Li XY, Du B, Kang HYJ, Wang YS, Wang F, Sun B, Tong ZH (2020) The keypoints in treatment of the critical novel coronavirus pneumonia patient. Zhonghua Jie He He Hu Xi Za Zhi 23:**43**–E022

Quinlan N et al (2011) Vulnerability: the crossroads of frailty and delirium. J Am Geriatr Soc 59(Suppl 2):S262–S268

Schoen JC, Erlandson KM, Anderson PL (2013) Clinical pharmacokinetics of antiretroviral drugs in older persons. Expert Opin Drug Metab Toxicol **9**:573–588

Yao H, Chen JH, Xu YF (2020) Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry **7**(4):e2