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Letter to the Editor

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Interest of clonidine for seven inpatient youths with intellectual disability and other severe neurodevelopmental disorders

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To the Editor,

There are few current data on the use of clonidine (CLO) in children and adolescents with intellectual disability (ID) and other neurodevelopmental disorders (NDD). CLO is an alpha-2 receptor agonist.[1] It can be used in the attention-deficit/hyperactivity disorder (ADHD) as a third-line pharmacotherapy in children and adolescent.[1] The rationale supposes that postsynaptic alpha-2-agonist stimulation regulates symptoms of hyperactivity, impulsivity, and inattention.[2,3] CLO has been reported to improve behavior disorders with ASD.[1]

In this letter, we present a series of 7 patients with intellectual disabilities and/or other NDDs complicated with severe psychiatric comorbidities, treated and improved by CLO.

All patients suffering from ID mild to profound (IQ from 54 to under 20) and other NDDs (ASD, genetic syndromic disorders, neurometabolic disorders, etc.) treated with CLO during hospitalization were included. ID was assessed by standardized psychometric tests: Kaufman Assessment Battery for Children (KABC-II), Wechsler Intelligence Scale for Children (WISC), and Wechsler Preschool and Primary Scale of Intelligence (WIPPSI) during or before hospitalization. Clinical improvement was based on clinical measures: the Clinical Global Impression Improvement scale (CGI-I) and the Children-Global Assessment Functioning (C-GAF) at entrance and at discharge. We classified and defined symptoms targeted by CLO as following: impulsivity, irritability, hyperactivity-psychomotor instability, and self-injurious behaviors (SIBs). The term "hyperactivity" is used as a descriptive symptom, not in a context of DSM-5-validated ADHD diagnosis, due to the existence of ID in all included patients. We purposely associated the term "psychomotor instability" with "hyperactivity." The improvement was based on the daily observations. Regarding CLO tolerance, heart rate and blood pressure were manually measured in 2 positions to capture orthostatic hypotension. After initial close monitoring, these variables were manually measured once a week in the morning until the end of the hospitalization. Any new side effect that could be imputable to CLO was recorded and reported.

This project was designated as Institutional Review Board exempt due to its retrospective design, patient de-identification, and the use of routine questionnaires. All families gave their consent after information.

Seven patients with ID aged between 5 and 17 years were reported and successfully treated with CLO (Table 1). Most patients were female. Discharge dosage ranged from 0.020 to 0.75 mg/day. During the hospitalization, all patients improved regarding the symptoms targeted by CLO. The 2 most frequent improved targeted symptoms were psychomotor instability (n = 6) and irritability (n = 3), followed by impulsivity (n = 1) and SIB (n = 1). Interestingly anxiety (n = 2) was also reported as improved in the medical file, even thought it was not defined as a primary targeted symptoms of CLO. We summarized different outcomes in Figure 1. Regarding the score of CGI and GAF, both showed improvement.

The main adverse effect identified was sedation in 1 patient (patient 2). It appears when 1 intake was added at lunchtime, with a total of 3 intakes (morning, lunch, and night). This last intake was withdrawn and sedation ceased.

Most of the patients received other medications, although they were treated with CLO. One patient received exclusively CLO; the others were also treated concomitantly with other psychotropic treatments. All details are to be found in Table 1.

The use of alpha-2 agonists as well as alpha-1 antagonists for aggression and agitation is of growing interest as treatment of acute agitation in adults with schizophrenia or bipolar disorder with molecules such as sublingual dexmetidomedine.[4,5] Therefore, we

Table 1. Case Descriptions

Patient	Age (y = years, mo = months)	Gender	Diagnosis	Symptoms targeted by clonidine	CGI-E	CGI-D	GAF-E	GAF-D	Treatment history before hospitalization	Treatments at discharge	CLO initial dose (mg/d)	Follow-up (mo)	Titration duration for full dose treatment (mo)	CLO discharge dose (mg/d)	Notable outcomes	Adverse effects
1	12 y	F	Mild ID (IQ 64), generalized anxiety disorder	Impulsivity ↓ Hyperactivity-psychomotor instability ↓ Irritability	13	5	55	85	ZUC, CYA, HYD, RIS, MET, ARI, LEV, TRO	BUS, CLO, MEL, LEV	0.15	2	1	0.750 (10 µg/kg/d)	Hyperactivity-psychomotor instability ↓ Anxiety ↓ Impulsivity	None
2	6 y 7 mo	M	ID, NDD (KABC-II: 2–3 y)	Impulsivity ↓ Hyperactivity-psychomotor instability ↓ Irritability	13	10	45	75	DES, RIS, MET, MEL, HYD, CYA, ARI, TIA	CLO, DES, MEL, LEV, TOP	0.075	10	6	0.125 (4 µg/kg/d)	Hyperactivity-psychomotor instability ↓ Impulsivity ↓ Irritability	Sedation at introduction ↓ Distribution with 2 intakes per day allowing better tolerance
3	9 y 2 mo	F	Mild ID (heterogeneous low IQ, not conclusive), NDD	Hyperactivity-psychomotor instability	13	5	50	85	MEL, MET, RIS	ARI, CLO, MEL, CYA	0.025	1	0	0.025 (1 µg/kg/d)	Irritability ↓ Hyperactivity-psychomotor instability ↓ Anxiety	None
4	7 y 2 mo	F	Severe ID (IQ 41), drug-resistant epilepsy, left ischemic stroke	Hyperactivity-psychomotor instability	13	10	75	90	LAM, LEVE, MET, ALI, TOP, ZON, RIS, MEL, VAL	CLO, MEL	0.025	1, 5	0.5	0.050 (2 µg/kg/d)	Hyperactivity-psychomotor instability ↓ Anxiety	None
5	17 y	F	Severe ID (IQ 45)	Hyperactivity-psychomotor instability ↓ Impulsivity	13	5	40	80	HAL, RIS, VAL, OLA, QUE	CLO, CLZ	0.075	2	1	0.15 (4 µg/kg/d)	Hyperactivity-psychomotor instability	None
6	6 y	M	Mild ID (IQ 60), Smith-Magenis syndrome	Self-injurious behaviors (picking++) ↓	13	5	55	90	None	CLO	0.015	2	1	0.030 (4 µg/kg/d)	Hyperactivity-psychomotor instability ↓	None

Table 1. *Continued*

Patient	Age (y = years, mo = months)	Gender	Diagnosis	Symptoms targeted by clonidine	CGI-E	CGI-D	GAF-E	GAF-D	Treatment history before hospitalization	Treatments at discharge	CLO initial dose (mg/d)	Follow-up (mo)	Titration duration for full dose treatment (mo)	CLO discharge dose (mg/d)	Notable outcomes	Adverse effects
				Hyperactivity-psychomotor instability											Self-injurious behaviors	
7	5 y	F	Severe ID (IQ 34) CDKL5 deficiency disorder: developmental epileptic encephalopathy	Irritability	13	10	45	75	VAL, Cannabidiol	VAL, CLO	0.010	2	1	0.020 (4 µg/kg/d)	Irritability ↓ Anxiety	None

Note: CGI-E: CGI at entrance; CGI-D: CGI at discharge; GAF-E: GAF at entrance; GAF-D: GAF at discharge.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALI, alimemazine; ANX, anxiety disorder; ARI, aripiprazole; BUS, buspirone; CLO, clonidine; CLZ, clozapine; CYA, cyamemazine; DES, desmopressine; HAL, haldol; HYD, hydroxizine; ID, intellectual disability; LEVO, levomepromazine; LEVE, levetiracetam, MEL, melatonine; MET, methylphenidate; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; TIA, tiapride; TOP, topiramate; TRO, tropatepine; VAL, valproate; ZON, zonisamide; ZUC, zuclopenthixol.

believe that serious consideration of agonist should also be given in pediatric settings, as alternate therapeutic option to antipsychotics. To the best of our knowledge, this series is the first to mainly focus on the interesting effect of CLO in pediatric patients with ID and other severe NDDs. Every patient clinically showed improvement in at least one of the targeted symptoms. Most of them (n = 6) improved regarding the psychomotor instability. CLO appears to enhance the activity in the prefrontal cortex, therefore allowing a better cognitive "filter," reducing the "frontal-like" behaviors. Interestingly, CLO had a positive effect on irritability and anxiety. This effect on mood disorders could be explained by the sedative and anxiolytic of alpha-2 agonists. We underline the idea that CLO may also be effective regarding anxiety and an interesting therapeutic option. We could extend this rationale to SIBs, given the strong participation of anxiety in SIBs. The other important data are the tolerance of CLO; overall, only one patient presented sedation at the introduction. This patient presented sedation at the beginning when optimal dosage was still being assessed. It is known that psychotropic drugs such as antipsychotics are often used, even at a very young age in pediatric population with ID or ASD. In addition to the efficacy reported here, the interesting property of CLO also stands in the absence of such metabolic side effects.

This use of CLO is not FDA-approved yet, and RCTs are mandatory to support our current results. Its use was possible after a written and signed consent of legal guardians. There are limits to our results. The number of patients is small with heterogeneous psychiatric profiles, even though they all shared the existence of ID and neurodevelopmental delay. The CLO dosage strategy was not standardized as no guideline exists; therefore, we only referred to previously described off-label use in ADHD and ASD. Most of the patients were receiving other treatments to address their behavioral symptoms which could bias the assessment of clinical response to CLO. Previous treatment appeared to be inefficient toward challenging symptoms at the time of their admission. Finally, the improvement was only assessed with general functioning scales GAF and CGI.

This case series underlines the therapeutic effect of CLO toward genuine challenging symptoms in youth with severe NDDs. Indeed CLO reduced psychomotor instability, impulsivity and most surprisingly improved anxiety manifestations. CLO could be an interesting first-line treatment for youth with NDD exhibiting agitation, impulsivity and anxiety before antipsychotic's use with good tolerance. Further RCTs are required to validate those aspects.

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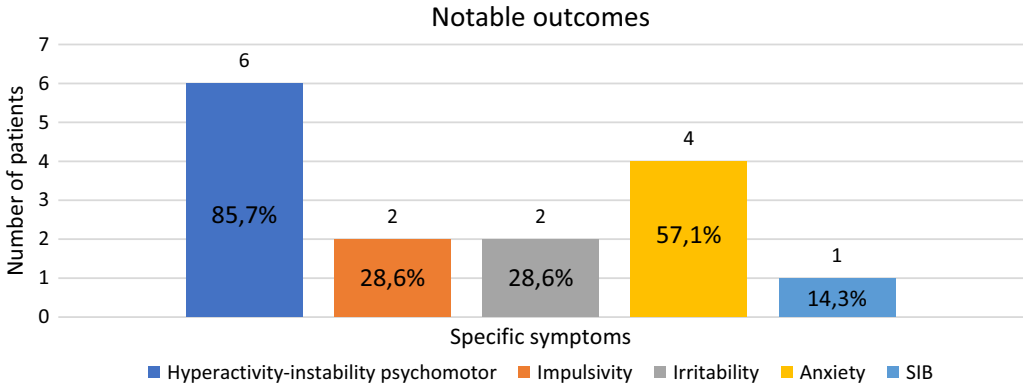

Figure 1. Notable outcomes after clonidine introduction.

Disclosure. The authors declare they have nothing to disclose.

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