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ORIGINAL CONTRIBUTION

Treatment use in a prospective naturalistic cohort of children and adolescents with catatonia

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Abstract We aimed to (1) describe the treatment used in a large sample of young inpatients with catatonia, (2) determine which factors were associated with improvement and (3) benzodiazepine (BZD) efficacy. From 1993 to 2011, 66 patients between the ages of 9 and 19 years were consecutively hospitalized for a catatonic syndrome. We prospectively collected sociodemographic, clinical and treatment data. In total, 51 (77 %) patients underwent a BZD trial. BZDs were effective in 33 (65 %) patients, who were associated with significantly fewer severe adverse events ($p = 0.013$) and resulted in fewer referrals for electroconvulsive therapy (ECT) ($p = 0.037$). Other treatments included ECT ($N = 12$, 18 %); antipsychotic medications, mostly in combination; and treatment of an underlying medical condition, when possible. For 10 patients, four different trials were needed to achieve clinical improvement. When all treatments were combined, there was a better clinical response in acute-onset catatonia ($p = 0.032$). In contrast, the response was lower in boys ($p = 0.044$) and when posturing ($p = 0.04$) and mannerisms ($p = 0.008$) were present as catatonic symptoms. The treatment response was independent of the underlying psychiatric or systemic medical condition. As in adults, BZDs should be the first-line symptomatic treatment for catatonia in young patients, and ECT should be a second option. Additionally, the absence of an association between the response to treatment and the underlying psychiatric condition suggests that catatonia should be considered as a syndrome.

Keywords Catatonia · Adolescence · Child · Pharmacological treatment · Benzodiazepine · Electroconvulsive therapy · Pharmacological treatment · Youth · Benzodiazepine · Electroconvulsive therapy

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Introduction

Catatonia is an unrecognized and severe psychiatric syndrome that includes psychological and motor symptoms. The symptoms can be continuous or discontinuous, and four different forms are described: stuporous, agitated, malignant and periodic [1, 2]. Catatonia may occur in adolescents and in children. The prevalence is estimated to range 0.6–17.7 % among young inpatients [1, 2]. In adults, catatonia is associated with psychiatric disorders (such as affective disorder and schizophrenia) and also medical conditions [3–7]. The clinical presentation of catatonia in children and adolescents is similar to that in adults, but three major differences should be noted. First, in juveniles, catatonia is more frequent in

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boys than in girls; second, schizophrenia is the most common underlying psychiatric condition [1– 3, 6, 8]. Third, a history of developmental disorders, such as pervasive developmental disorder (PDD) and intellectual disability (ID), can also be associated with catatonia [9, 10]. Catatonia is one of the most severe psychiatric disorders in children and adolescents, as this condition increases the risk of premature death (including by suicide) 60-fold [11].

In adults, benzodiazepines (BZDs) and zolpidem have proven to be efficient treatments for catatonia, and a high dose is currently used to treat severe forms [12–14]. Certain authors recommend a therapeutic test with a BZD (at a high dosage when a low dose is not efficient) when a catatonic syndrome is clinically suspected [13, 15]. According to Rosebush et al., once catatonic symptoms improve, an antipsychotic (AP) may be started cautiously, despite the fact that antipsychotics can worsen symptoms in acute catatonia with a risk of malignant catatonia [16–18]. In the case of a negative response to BZDs and/or a life-threatening condition, electroconvulsive therapy (ECT) is a valid option [3, 13, 19, 20]. In the case of insufficient efficacy of BZDs and ECT and according to the underlying psychiatric condition, an atypical AP associated with a BZD may be introduced [15, 16]. Very few studies exist regarding pharmacological treatment of catatonia in children and adolescents. Moreover, it seems that there is a lack of knowledge of BZD efficacy among physicians in charge of the pediatric population (e.g., in the context of catatonia associated with a medical condition) [4]. Moreover, BZD is not recommended in the pediatric population given the adverse effect profile (e.g., paradoxical response or addiction). Most of the literature is limited to case reports exploring the use of specific medications (e.g., zolpidem [21], BZDs [2, 22–24], glutamate antagonists [19, 25]), adjuvant treatment (e.g., packing [26] or ECT [27– 29], particularly in the context of agitated or malignant catatonia [30– 33]. Regarding ECT, a literature review reported that among 59 children and adolescents with catatonia, 45 (76 %) patients responded to this treatment [20].

We prospectively followed up a sample of juvenile patients with catatonia from 1993 to present to investigate their sociodemographic characteristics, symptomatology, associated psychiatric and medical conditions, developmental histories and treatment responses [1, 11, 34]. This study aimed (1) to describe the treatment used in this sample of 66 young patients with catatonia (both treatment for catatonic symptoms and treatment for associated medical and psychiatric conditions are reported), (2) to determine which factors were associated with improvement and (3) to identify specific factors associated with BZD efficacy.

Method

Participants

We assessed all patients admitted to the Department of Child and Adolescent Psychiatry at University Hospital La Pitié-Salpêtrière between 1993 and 2011 for catatonia. In total, we hospitalized 5,532 patients aged 4–18 years. To receive a diagnosis of catatonia, patients had to present at least two motor symptoms or one motor symptom and one non-motor symptom indicative of severe behavioral and emotional impairment. The catatonic symptom list was based on a modified version of the Bush and Francis scale [1, 34–36]. We excluded patients who presented extrapyramidal syndrome secondary to antipsychotics from participation. Recruitment details are available in previous publications [1, 11, 37]. During the inclusion period, previous reports created more attention and interest in the syndrome, leading to a higher frequency of recruitment due to transfer from other French units after 2006 (40 versus 26 inclusions after and before 2006, respectively). This change corresponds to the opening of the French National Centre for Psychiatric Rare Diseases and Catatonia in the Department of Child and Adolescent Psychiatry at University Hospital La Pitié-Salpêtrière. We included 66 patients in this sample, aged 9–19 years. The study was conducted according to the hospital ethics committee's regulations. The follow-up clinical data of a subsample have been previously published [11], and a paper focusing on patients' medical conditions and developmental history was published in 2012 [6].

Patient assessment

We conducted a systematic assessment within the patients' first week of admission and repeated this assessment at discharge. This assessment included (1) collection of sociodemographic data (age, sex, country of origin and family socioeconomic status (SES)); (2) a semi-structured interview to evaluate patients' personal and family histories of psychiatric and medical disorders (detailed in (Taieb et al., 2002) [38]); (3) a clinical examination; (4) administration of a modified version of the Bush and Francis scale to test for the presence and severity of catatonic symptoms [1, 34–36]; the scale is rate of each patient at admission and at discharge; (5) use of the Clinical Global Impression-Severity scale (CGI-S) [39] and the Global Assessment Functioning scale (GAF) to assess patients' clinical severity at admission and discharge; and (6) collection of information on the duration of the psychiatric episode, the duration of hospitalization, the type of catatonia onset (e.g., <10 days = acute; ≥ 10 days = insidious), the duration of acute catatonia and the type of catatonia (e.g., episodic or chronic). We considered

catatonia as chronic if the patient had catatonic symptoms after discharge from the index episode; (7) Treatments such as pharmacological treatments, ECT and all other types of medical intervention (e.g., plasma exchanges) were reported prospectively. BZD efficacy was also reported using the CGI-Improvement scale (CGI-I).

We diagnosed psychiatric conditions associated with catatonia according to the DSM-IV criteria. The Diagnostic Interview for Genetic Studies (DIGS) version 2.0, a semi-structured diagnostic interview developed by the Human Genetics Initiative of the National Institute of Mental Health, assessed lifetime and current psychiatric diagnoses (www.nimhgenetics.org; French translation by CL). The DIGS elicits the information necessary to diagnose psychotic, mood, anxiety, substance use and eating disorders as well as suicidal behaviors using the DSM-IV criteria. We interviewed most patients after the acute phase of their illness. To maximize the accuracy of our psychiatric diagnoses, we obtained clinical information from each patient's regular psychiatrist. Based on all available information, the consensus reached by the patient's treating clinician, the DIGS interviewer and one additional child/adolescent psychiatrist (DC or AC) were used to diagnose patients. In cases of ID or PDD, we confirmed diagnoses using the parental Autism Diagnostic Interview—Revised [40] and the Wechsler Intelligence Scales. Both scales are used routinely in the department. If we confirmed an ID or PDD diagnosis, a geneticist performed a systematic clinical and molecular evaluation, including karyotyping and a search for 22q11 and 15q11–q13 chromosomal abnormalities by FISH in all patients and a search for Fragile X in boys (if the patient had never undergone this assessment). A physical examination was performed on all patients. In previous reports, we proposed guidelines for clinical and paraclinical investigations to help to determine the medical conditions associated with catatonia [4, 41].

Treatment variable

For every patient, data on pharmacological, ECT and specific treatments for medical conditions during hospitalization were prospectively collected. Medication classes were defined based on the European Pharmaceutical Market Research Association (EphMRA) classification: classical and atypical antipsychotics, mood stabilizers and antidepressants. For the use of BZDs, we considered the following items: (1) the use of BZDs in catatonic syndrome, (2) the type of BZDs, (3) the use of BZDs alone or in association with other psychiatric treatments, (4) the efficacy of BZDs ("much improved" or "very much improved" on the CGI-I) and (v) the presence of severe adverse events affecting prescription (e.g., severe sedation preventing a dose increase; or respiratory distress requiring BZD to be stopped). The efficacy of BZD treatment was assessed by the senior clinician who was not blind to diagnosis. The dosage of BZDs was adapted by the same clinician according to clinical response. We used a 7.5 mg equivalent of the lorazepam threshold to define low and high dosages.

The treatment algorithm in this natural clinical context used the following procedure. Patients received a first line of treatment. A lack of a response or a poor response and/or severe adverse events led to the use of a second line of treatment. This procedure was repeated for a maximum of four lines of treatment. For each line of treatment, we observed the use of the EphMRA-classified drugs indicated above. We also recorded the combination of two or more treatments from this list and the presence of adverse events. ECT data were also collected from the anesthesiology charts, including (1) the onset of ECT (first, second or third line of treatment) and (2) the number of ECT sessions. Each processing line can find different type of treatments (Classical Antipsychotic, APc, Atypical Antipsychotic APa, clozapine, Mood Stabilizer MS, Antidepressant AD, a Benzodiazepine BZD or ECT) alone or combined. Treatments used at least 15 days have been taken into account. The BZD is not always introduced in first intention.

Statistical analysis

All statistical analyses were performed using R 2.12.2 (The R Foundation for Statistical Computing) and two-tailed tests considering $p \leq 0.05$ as significant. Student's t tests were used to make two-group comparisons when data were normally distributed (with a Welch correction in the case of heteroscedasticity); otherwise, Mann–Whitney's U test was used. To evaluate the association between qualitative variables, Fisher's exact test was used. In the case of two dichotomous variables, odds ratios (ORs) were calculated with their corresponding 95 % confidence intervals (CIs). When all treatments were combined, treatment efficacy was assessed using the catatonia rating scale scores at admission and discharge. "Very much improved" was defined as a catatonia score decrease reaching a discharge score <10. "Much improved" was defined as a catatonia score decrease but a discharge score ≥ 10. Otherwise, patients were not improved.

Results

Sociodemographic and clinical characteristics

The sample included 23 females (35 %) and 43 males (65 %) with a mean age of 14.89 (range 9–19). We found

no relationship between SES catatonia. Regarding underlying psychiatric conditions, 38 (58 %) patients suffered from schizophrenia; 11 (17 %) patients, from mood disorders; 17 (26 %) patients, from pervasive developmental disorder; and 8 (12 %) patients from intellectual disability. An underlying medical condition was present among 16 (24 %) patients. The high severity scores obtained on different clinical scales (CGI, EGF and Catatonic scale) at admission confirmed that the present cohort was composed of severely impaired patients. The mean duration of hospitalization was 21 weeks. In this cohort more than half of the cases were of non-European origin (compared to approximately 20 % of all inpatients in the study sites born of immigrant parents). The literature on adults [42, 43] suggests that ethnic and/or cultural factors may play a role in the clinical expression of catatonia. Given the high prevalence of catatonia—17 %—in child and adolescent psychiatric patients in India, which contrasts with the rate estimated by Cohen et al. [1], cultural factors may also play a role in catatonic manifestations [2]. However, a selection bias may explain some of the differences in cultural prevalence and future studies should consider this in their sampling. Cross-cultural comparative studies of childhood catatonia would be very informative in clarifying the role of cultural factors in the expression of catatonia in children and adolescents. Complete sociodemographic and clinical data are summarized in Table 1.

Table 1 Clinical and socio-demographic characteristics of childs and adolescents hospitalized for catatonic syndrome

Socio-demographic characteristics		
Sex *N* (%)		43 males (65 %)/23 females (35 %)
Age mean ± SD [range]		14.8 years ± 2.5
Socio-economic status		
Low *N* (%)		26 (39 %)
Middle *N* (%)		18 (27 %)
High *N* (%)		22 (33 %)
Paternal origin		
France (mainland) *N* (%)		22 (33 %)
Migrants *N* (%)		44 (67 %)
Maternal origin		
France (mainland) *N* (%)		27 (41 %)
Migrants *N* (%)		39 (59 %)
Diseases associated to catatonic syndrome		
Psychiatric diagnosis		
EDM *N* (%)		19 (29 %)
Schizophrenia *N* (%)		38 (58 %)
PDD *N* (%)		17 (26 %)
Manic or mixed episode *N* (%)		5 (8 %)
Schizoaffective *N* (%)		4 (6 %)
Disorder intellectual disability *N* (%)		8 (12 %)
Brief psychotic episode N(%)		3 (5 %)
Bipolar disorder *N* (%)		11 (17 %)
Other		1 (2 %)
Medical condition N (%)		16 (24 %)
Severity scales mean ± SF [range]		
	Scores at admission	Score at discharge
EGF	18.29 ± 7.06 [10, 35]	51.18 ± 14.46 [30;80]
CGI-S	6.65 ± 0.74 [4, 7]	4.30 ± 1.57 [1; 7]
Catatonia	21.01 ± 6.44 [9, 38]	7.82 ± 6.22 [0;28]

CGI-S Clinical global impression—severity, *GAF* global assesment of functioning, *EDM* major depressive episode, *PDD* perseverative developmental disorder

Treatment of catatonia with BZDs

Among the 66 patients in the sample, 51 (77 %) received BZDs (lorazepam: $N = 38$; clonazepam: $N = 6$; clorazepam: $N = 6$; and prazepam: $N = 1$). BZD treatment was efficient for 33 (65 %) patients and inefficient for 18 (35 %) patients. The average dose of lorazepam was 5.35 ± 3.64 mg/day (range [2, 15]). In total, 47 (92 %) patients received BZDs in association with other psychotropic treatment, and 4 (8 %) patients received BZDs alone. Severe adverse events due to BZDs were rare; only 6 (12 %) patients had severe adverse events. The encountered adverse events were leukopenia, excessive sedation ($N = 3$), a respiratory distress episode (in one patient with fatal familial insomnia) and agitation.

Treatment at discharge

At discharge, 15 patients still received BZDs (lorazepam: $N = 11$; clonazepam: $N = 2$, and for 1 of the 2 patients, clonazepam was used as an anticonvulsant; and diazepam: $N = 1$). Two patients were not given psychotropic treatment because their pharmacological treatment targeted the underlying medical condition (lupus). Three patients received non-pharmacological treatment at discharge: because one left the department without medical authorization, one who died of fatal familial insomnia and one for whom maintenance ECT was the only treatment at discharge. In total, 25 patients received a single treatment (Classical Antipsychotic, APc, Atypical Antipsychotic APa, clozapine, Mood Stabilizer MS, Antidepressant AD or a Benzodiazepine BZD), 28 patients received a combination of two treatments and 8 patients were given a combination of three treatments. One patient received a combination of an anticonvulsant and a BZD; in this case, a BZD was administered due to its anticonvulsant properties. Five patients received clozapine: one as unique treatment and four in combination with another treatment. Clozapine was given neither as a first-line nor as a second-line treatment as requested by French regulation rules. A severe

adverse event was observed for one patient (tachycardia). Details of the pharmacological treatments and the combinations of treatments at discharge are shown in Table 2.

In total, 12 (18 %) patients received ECT, including 3 patients requiring ECT as a first line of treatment: two patients had a severe condition (Malignant catatonia); one patient failed to respond to an adequate BZD trail in another department and was transferred to receive ECT in our department. In two cases among the other cases who received ECT, ECT was considered despite improvement with BZD treatment, because of a severe and potentially lethal condition. One patient received maintenance ECT for intractable catatonic schizophrenia [27]. Electrode placement is bilateral, and frequency during the acute course is between two and three sessions per week.

Sixteen of the 66 patients suffered from medical conditions. Certain medical conditions had no treatment (e.g., Huntington disease). Other patients were administered a specific treatment (e.g., plasma exchange and immunosuppressive treatment in the case of autoimmune disease) [44].

Lines of treatment

Figure 1 shows the flow diagram of different lines of treatments. A first line of treatment was sufficient for 17 (26 %) patients. A second line of treatment was required for 49 patients, and 33 received definitive treatment. A third line of treatment was required for 16 patients, and 6 received definitive treatment. A fourth line of treatment was required for 10 patients, and 9 had a good therapeutic response. Among the 12 patients who received ECT, 5 patients required treatment adaptation after ECT sessions: 3 of these patients had received ECT from the beginning, and 2 patients had received ECT as a second line of treatment.

Variables associated with improvement

BZD treatment was efficient for 65 % of the subjects. The dosages were much higher than those currently recommended for the pediatric population, with doses up to 15 mg/day. There was no association between doses (high doses $\geq$7.5 mg versus low doses <7.5 mg lorazepam), and efficacy as reflected by "much improved" and "very much improved" on the CGI-I (mean = 5.3 mg (SD = 3.5) in responders versus mean = 5.9 mg (SD = 4.3) in non-responders; $U = 193.5$; $p = 0.9$). The efficacy of BZDs was significantly associated with fewer severe side effects (OR = 0.1, 95 % CI [0; 0.64], $p = 0.013$), and with less treatment with electroconvulsive therapy (OR = 0.2, 95 % CI [0.03; 0.92], $p = 0.037$).

Regarding all treatment combined and the catatonia score at discharge, there were no sociodemographic data significantly associated with treatment response (catatonia score <10 at discharge) except gender. The proportion of boys who were very much improved was three times less than the proportion of girls (OR = 0.3, 95 % CI [0.08; 0.97], $p = 0.044$). No significant association was found between catatonia improvement and the underlying psychiatric or systemic medical condition. Acute onset of catatonia was associated with a better clinical response: there were three times more very much improved patients with acute onset than with insidious onset (OR = 3.3, 95 % CI [1.1; 11.1], $p = 0.032$). Additionally, lower catatonia scores at admission were associated with a better clinical

Table 2 Pharmacological treatment for in patient with catatonia at discharge

	Number of patient (%)
Medication	
No psychotropic treatment	2 (3 %)
One treatment received	25 (38 %)
Combination of 2 treatments	23 (42 %)
Combination of 3 treatments	8 (12 %)
Pharmacological classes	
One treatment received	
APc	12
APa	9
Clozapine	1
MS	2
BZD	1
Combination of 2 treatments	
APc + MS	6
APa + MS	4
APa + AD	4
APc + APa	1
APa + Clozapine	1
AD + MS	1
APc + BZD	4
APa + BZD	3
Clozapine + BZD	2
AD + BZD	1
AntiC + BZD	1
Combination of 3 treatments	
APa + MS + AD	1
APc + MS + AD	1
APc + APa + MS	1
APa + MS + BZD	1
APa + AD + BZD	2
APa + APc + AD	1
Clozapine + APc + MS	1

APa atypical antipsychotic, *APc* classical antipsychotic, *AntiC* anticonvulsivant, *AD* antidepressant, *MS* mood stabilisator, *BZD* benzodiazepine 3 patients (5 %) did not received pharmacological treatment

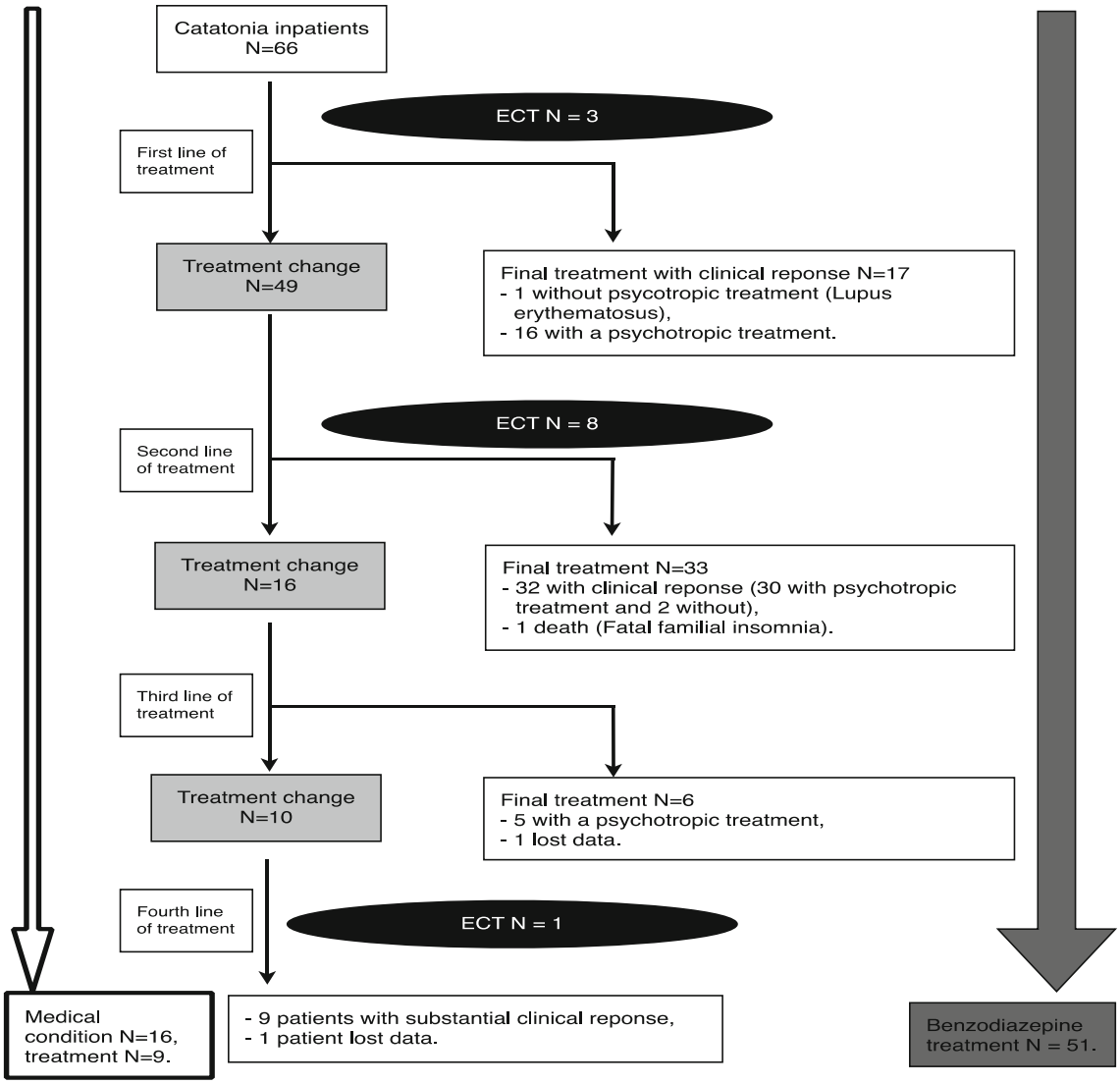

Fig. 1 Diagram flow

response (mean = 22.8 (SD = 6.6) for "no improvement" or "much improved" versus mean = 19.2 (SD = 6.1) for "very much improved"; $U = 2.25$; $p = 0.028$). Regarding catatonic symptoms, posturing and mannerism were associated with a lower clinical response. The proportion of patients who were very much improved was three times lower when patients showed posturing than when they did not (OR = 0.3; 95 % CI [0.06; 0.95]; $p = 0.04$). The proportion of patients who were very much improved was five times lower when patients showed mannerism than when they did not (OR = 0.2; 95 % CI [0.04; 0.69]; $p = 0.008$).

Discussion

This prospective study aimed to describe treatments used in catatonia and their efficacy in an inpatient setting. As in adults, we found a high rate (65 %) of symptomatic response to BZDs when treating catatonia. No correlation was found between the underlying condition and BZD efficacy or, more broadly, between global treatment efficacy and catatonia improvement. Evidence of efficient symptomatic treatment leads to the consideration of catatonia as a syndrome [28] and supports the recent changes proposed in DSM5 classification. Moreover, BZD dosages were not correlated with efficacy although some patients required high doses, and among patient responders to BZDs, fewer side effects were observed, and ECT was less frequently needed. Hence, as in adults, we recommend using BZDs as a first-line treatment, started at low doses and increased until a minimal efficient dose is reached. In the adult population, high doses of BZDs are often recommended [3, 45, 46]. The appropriate dosage may be different in juveniles. It is likely that the pharmacokinetic

characteristics of BZDs in the pediatric population are involved in this difference [47, 48]. Moreover, it is likely that young patients do not tolerate high dosages in the same way, given the significant association we found between severe adverse events and a lack of a clinical response.

ECT appeared to be a second-line treatment when BZD efficiency was not sufficient or when secondary effects prevented an increase in doses. ECT was a safe and efficient treatment for catatonia, as reported in most case reports published so far [14, 20, 32]. In this sample, ECT was used in patients resistant to the first-line treatment or in patients with extremely severe psychiatric conditions. Thus, ECT occurrence and BZD efficacy were negatively associated in this sample. In clinical practice, ECT is reserved in most cases for patients who fail to respond to BZDs. There is certain resistance to using such a treatment among young patients, most likely because of the lack of data on the consequences of seizure on a developing brain [49] and on the mechanism underlying the efficacy of ECT; the invasive characteristic of the treatment [50]; and irrational fears regarding ECT, including among relatives [51]. Although the use of ECT raises ethical issues (e.g., the collection of informed consent from minor patients), a careful ethical debate on the use of ECT in the adolescent population following general principles in medical ethics, such as autonomy, beneficence, non-malfeasance, justice and cautiousness, showed that severely impaired adolescents today are at a greater risk if they do not receive ECT [38, 50].

Regarding the improvement of catatonia, posturing and mannerism were negatively associated with clinical response. Interestingly, posturing has been associated with resistance to catatonia treatment in adults. Ungvari et al. [52] showed that non-responders to treatment presented a higher rate of waxy flexibility and posturing. Additionally, sex was the only sociodemographic variable that was significantly associated with BZD efficacy as the clinical response in boys was significantly lower than in girls. This was not due to differences in BZDs dosage between boys and girls. Several hypotheses may be proposed to understand this association. First, there is more developmental history (pervasive developmental disorder and/or intellectual disability) and more early-onset schizophrenia among boys. Second, episodes of early-onset schizophrenia associated with catatonia appear to be more severe than episodes of early-onset schizophrenia without catatonia [53]. Third, the lower frequency of clinical response among boys may be related to the existence of a subgroup of boys presenting severe chronic catatonic schizophrenia, as evidenced in a previous follow-up study that we conducted on a subsample [11]. Notably, first these patients showed high rates of mannerism (OR = 5.7; 95 % CI [1.6; 22.4]; $p = 0.00446$), and second the patient who needed maintenance ECT belonged to this subgroup.

The current study has several clinical implications. As Fink and Taylor highlighted in 2003 based on their experience in treating adult catatonia and on the limited body of literature regarding catatonia in the pediatric population, symptomatic treatment of catatonia in juveniles should not differ from symptomatic treatment in adults [3]. Also, the reluctance to prescribe BZDs in young patients should not prevent their use in case of pediatric catatonia. To summarize the results presented here and other recent studies, we should note the following: (1) the positive clinical response to BZD trials and ECT, (2) the risk of using atypical or typical antipsychotic drugs because of a switch to malignant catatonia and (3) the benefits of searching for and treating underlying medical and psychiatric conditions [6, 13, 19, 54, 55].

Based on our early experience with catatonia in children and adolescents, we previously proposed a treatment algorithm for young patients [37]. The clinical relevance of the algorithm is concordant with the current results. First, we recommend assessing patients during hospitalization, monitoring catatonia severity with appropriate rating scales, determining underlying psychiatric and medical conditions and using BZDs as a first-line symptomatic treatment. ECT must be considered in case of failure of the first-line treatment. We propose to add a specific treatment regarding the underlying psychiatric condition (e.g., APa in the case of schizophrenia, with caution because of the risk of malignant catatonia). Additionally, when a medical condition is found, it should eventually be treated (e.g., plasma exchange and immunosuppressive medication in the case of autoimmune disease). In juveniles, the search for a medical condition is a major challenge, as the frequency can reach 20 % [6].

The results of the current study should be interpreted in the context of its limitations and strengths. The main limitations are as follows: (1) The low number of patients despite the large period of recruitment (19 years), which is explained by the low prevalence of catatonia in juveniles [1, 2, 8]. (2) Given the number of variables implicated, it was not valid to use multivariate analysis because of a lack of statistical power. (3) Treatment efficacy was not assessed under blinded conditions. (4) The treatment was not standardized, except the recommendation of a BZD trial in the late 1990 s. The strengths of this study include (1) the large amount of data and the prospective design, (2) the recruitment of participants over a 19-year period, (3) the length of hospitalization during which patients were assessed and treated and (4) the fact that this sample is the largest in the literature.

Conclusion

In children and adolescents, as in adults, BZDs should be the first-line symptomatic treatment for catatonia, and ECT

is a second option. Additionally, the absence of an association between the response to treatment and the underlying psychiatric or systemic medical condition suggests that catatonia should be considered as a syndrome as proposed in the DSM5.

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conflict of interest During the last two years, Dr. Cohen reported past consultation for or the receipt of honoraria from Bristol-Myers Squibb, Otsuka, Shire, Lundbeck and IntegraGen. Dr Consoli reported receiving travel support from BMS. No other authors reported financial disclosure or conflict of interest.

References

1. Cohen D, Nicolas JD, Flament MF, Perisse D, Dubos PF, Bonnot O et al (2005) Clinical relevance of chronic catatonic schizophrenia in children and adolescents: evidence from a prospective naturalistic study. Schizophr Res 76(2–3):301–308
2. Thakur A, Jagadheesan K, Dutta S, Sinha VK (2003) Incidence of catatonia in children and adolescents in a paediatric psychiatric clinic. Aust N Z J Psychiatry 37(2):200–203
3. Taylor MA, Fink M (2003) Catatonia in psychiatric classification: a home of its own. Am J Psychiatry 160(7):1233–1241
4. Lahutte B, Cornic F, Bonnot O, Consoli A, An-Gourfinkel I, Amoura Z et al (2008) Multidisciplinary approach of organic catatonia in children and adolescents may improve treatment decision making. Prog Neuropsychopharmacol Biol Psychiatry 32(6):1393–1398 Epub 2008 Mar 7
5. Cottencin O, Warembourg F, de Chouly de Lenclave MB, Lucas B, Vaiva G, Goudemand M et al (2007) Catatonia and consultation-liaison psychiatry study of 12 cases. Prog Neuropsychopharmacol Biol Psychiatry 31(6):1170–1176 Epub 2007 Apr 19
6. Consoli A, Raffin M, Laurent C, Bodeau N, Campion D, Amoura Z et al (2012) Medical and developmental risk factors of catatonia in children and adolescents: a prospective case-control study. Schizophr Res 137(1-3):151–158. doi:10.1016/jschres201202012 Epub 2012 Mar 7
7. Fink M (1011) Rediscovering catatonia: the biography of a treatable syndrome. Acta Psychiatr Scand Suppl 2013(441):1–47. pii:11/acps12038
8. Takaoka K, Takata T (2003) Catatonia in childhood and adolescence. Psychiatry Clin Neurosci 57(2):129–137
9. Dhossche DM (2004) Autism as early expression of catatonia. Med Sci Monit 10(3):RA31–RA39 Epub 2004 Mar 1
10. Wing L, Shah A (2000) Catatonia in autistic spectrum disorders. Br J Psychiatry 176:357–362
11. Cornic F, Consoli A, Tanguy ML, Bonnot O, Perisse D, Tordjman S et al (2009) Association of adolescent catatonia with increased mortality and morbidity: evidence from a prospective follow-up study. Schizophr Res 113(2–3):233–240 Epub 2009 May 13
12. Caroff mf. Catatonia: from psychopathologyto neurobiology. Washington (DC): American Psychiatric Press 2004
13. Fink T (2003) Catatonia: a clinician's guide to diagnosis and treatment. Cambridge University Press, Cambridge (GB)
14. Dhossche DM (1010) Wachtel LE (2010) Catatonia is hidden in plain sight among different pediatric disorders: a review article. Pediatr Neurol 43(5):307–315. pii:16/jpediatrneurol201007001
15. Rosebush PI, Mazurek MF (2009) Catatonia and its treatment. Schizophr Bull
16. Van Den Eede F, Van Hecke J, Van Dalfsen A, Van den Bossche B, Cosyns P, Sabbe BG (2005) The use of atypical antipsychotics in the treatment of catatonia. Eur Psychiatry 20(5–6):422–429
17. Pommepuy N, Januel D (2002) Catatonia: resurgence of a concept. A review of the international literature. Encephale 28(6 Pt 1):481–492
18. Huang TL, Ree SC, Huang YC, Liu HY, Yang YY (1999) Catatonic features: differential diagnosis and treatments at an emergency unit. Psychiatry Clin Neurosci 53(1):63–66
19. LE Wachtel, Hermida A, Dhossche DM (2010) Maintenance electroconvulsive therapy in autistic catatonia: a case series review. Prog Neuropsychopharmacol Biol Psychiatry 34(4):581–587. doi:10.1016/jpnpbp201003012 Epub 2010 Mar 16
20. Consoli A, Benmiloud M, Wachtel L, Dhossche D, Cohen D, Bonnot O (2010) Electroconvulsive therapy in adolescents with the catatonia syndrome: efficacy and ethics. J ECT 26(4):259–265. doi:10.1097/YCT0b013e3181fb3924
21. Zaw ZF, Bates GD (1997) Replication of zolpidem test for catatonia in an adolescent: Lancet. 349(9069):1914
22. Menard ML, Yagoubi F, Drici M, Lavrut T, Askenazy F (2013) Follow-up of a 16-year-old adolescent with early-onset schizophrenia and catatonic symptoms. Encephale 39(Suppl 1):S29–S35. doi:10.1016/jencep201208007 Epub 2012 Dec 6
23. Saito S, Yamaga K, Kobayashi T, Kato S (2011) A case of Asperger's disorder with catatonia originally suspected of being catatonic schizophrenia. Seishin Shinkeigaku Zasshi 113(3):241–247
24. Mukai Y, Two A, Jean-Baptiste M (2011) Chronic catatonia with obsessive compulsive disorder symptoms treated with lorazepam, memantine, aripiprazole, fluvoxamine and neurosurgery. BMJ Case Rep. doi:10.1136/bcr0220113858
25. McDaniel WW, Spiegel, Sahota AK (2006) Topiramate effect in catatonia: a case series. J Neuropsychiatry Clin Neurosci 18(2):234–238
26. Consoli A, Gheorghiev C, Jutard C, Bodeau N, Kloeckner A, Pitron V et al (2010) Lorazepam, fluoxetine and packing therapy in an adolescent with pervasive developmental disorder and catatonia. J Physiol Paris 104(6):309–314. doi:10.1016/jjphysparis201009002 Epub 2010 Oct 1
27. Consoli A, Boulicot V, Cornic F, Fossati P, Barbeau M, Cohen D (2009) Moderate clinical improvement with maintenance ECT in a 17-year-old boy with intractable catatonic schizophrenia. Eur Child Adolesc Psychiatry 18(4):250–254. doi:10.1007/s00787-008-0724-6 Epub 2009 Jan 20
28. Weiss M, Allan B, Greenaway M (2012) Treatment of catatonia with electroconvulsive therapy in adolescents: J Child Adolesc Psychopharmacol. 22(1):96–100. doi:10.1089/cap.2010.0052
29. LE Wachtel, Dhossche DM, Reti IM, Hughes-Wheatland R (2012) Stability of intellectual functioning during maintenance electroconvulsive therapy. Pediatr Neurol 47(3):219–221. doi:10.1016/jpediatrneurol201205012
30. Slooter AJ, Braun KP, Balk FJ, van Nieuwenhuizen O, van der Hoeven J (2005) Electroconvulsive therapy for malignant catatonia in childhood. Pediatr Neurol 32(3):190–192
31. Dhossche DM, Shettar SM, Kumar T, Burt L (2009) Electroconvulsive therapy for malignant catatonia in adolescence. South Med J 102(11):1170–1172
32. Zaw FK (2006) ECT and the youth: catatonia in context. Int Rev Neurobiol 72:207–231

33. Cohen D, Cottias C, Basquin M (1997) Cotard's syndrome in a 15-year-old girl. Acta Psychiatr Scand 95(2):164–165
34. Cohen D, Flament M, Dubos P, Basquin M (1999) The catatonic syndrome in young people. J Am Acad Child Adolesc Psychiatry 38(8):1040–1106
35. Bush G, Fink M, Petrides G, Dowling F, Francis A (1996) Catatonia. I. Rating scale and standardized examination. Acta Psychiatr Scand 93(2):129–136
36. Ey H (1950) Etudes psychiatriques. Desclée de Brouwer & Cie, Paris
37. Cornic F, Consoli A (2007) Catatonia in child and adolescent. Psychiatr Ann 37(1):19–26
38. Taieb O, Flament MF, Chevret S, Jeammet P, Allilaire JF, Mazet P et al (2002) Clinical relevance of electroconvulsive therapy (ECT) in adolescents with severe mood disorder: evidence from a follow-up study. Eur Psychiatry 17(4):206–212
39. Guy W (1976) ECDEU assessment manual for psychopharmacology. National Institute of Mental Health, Bethesda
40. Lord C, Rutter M, Le Couteur A (1994) Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24(5):659–685
41. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D (2007) Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis 30(5):631–641 Epub 2007 Aug 10
42. Leff J (1981) Psychiatry around the world: a transcultural view. Marcel Dekker Inc., New York
43. Varma V (1992) Transcultural Psychiatry. In: postgraduate Medecine, pp 611–35. Churchill Livingston, New Dehli
44. Marra D, Amoura Z, Soussan N, Haroche J, Consoli A, Ghillami-Dalbin P, et al (2008) Plasma exchange in patients with stuporous catatonia and systemic lupus erythematosus: Psychother Psychosom 77(3):195–6. doi: 10.1159/000120280. Epub 2008 Mar 10
45. Fink M (2009) Catatonia: a syndrome appears, disappears, and is rediscovered. Can J Psychiatry 54(7):437–445
46. Fink M, Taylor MA (2009) The catatonia syndrome: forgotten but not gone. Arch Gen Psychiatry 66(11):1173–1177
47. Crom WR, Relling MV, Christensen ML, Rivera GK, Evans WE (1991) Age-related differences in hepatic drug clearance in children: studies with lorazepam and antipyrine. Clin Pharmacol Ther 50(2):132–140
48. Pichini S, Papaseit E, Joya X, Vall O, Farre M, Garcia-Algar O et al (2009) Pharmacokinetics and therapeutic drug monitoring of psychotropic drugs in pediatrics. Ther Drug Monit 31(3):283–318. doi:10.1097/FTD0b013e31819f3328
49. Rey JM, Walter G (1997) Half a century of ECT use in young people. Am J Psychiatry 154(5):595–602
50. Cohen D, Flament M, Taieb O, Thompson C, Basquin M (2000) Electroconvulsive therapy in adolescence. Eur Child Adolesc Psychiatry 9(1):1–6
51. Taieb O, Flament MF, Corcos M, Jeammet P, Basquin M, Mazet P et al (2001) Electroconvulsive therapy in adolescents with mood disorder: patients' and parents' attitudes. Psychiatry Res 104(2):183–190
52. Ungvari GS, Chiu HF, Chow LY, Lau BS, Tang WK (1999) Lorazepam for chronic catatonia: a randomized, double-blind, placebo-controlled cross-over study. Psychopharmacology 142(4):393–398
53. Bonnot O, Tanguy ML, Consoli A, Cornic F, Graindorge C, Laurent C et al (2008) Does catatonia influence the phenomenology of childhood onset schizophrenia beyond motor symptoms? Psychiatry Res 158(3):356–362 Epub 2008 Feb 12
54. Perisse D, Amoura Z, Cohen D, Saintigny P, Mekhloufi F, Mazet P et al (2003) Case study: effectiveness of plasma exchange in an adolescent with systemic lupus erythematosus and catatonia. J Am Acad Child Adolesc Psychiatry 42(4):497–499
55. Consoli A, Ronen K, An-Gourfinkel I, Barbeau M, Marra D, Costedoat-Chalumeau N et al (2011) Malignant catatonia due to anti-NMDA-receptor encephalitis in a 17-year-old girl: case report. Child Adolesc Psychiatry Ment Health 5(1):15. doi:10.1186/1753-2000-5-15