CONTROL OF PSYCHOMOTOR AGITATION AND AGGRESSIVE BEHAVIOR IN PATIENTS WITH AUTISTIC DISORDER

A retrospective chart review

Camila Marinho Novaes[1], Milena Pereira Pondé[2], Antonio Carlos Cruz Freire[3]

Abstract – **Objective**: To evaluate the efficacy of pharmacotherapy on the symptoms of psychomotor agitation and aggressive behavior in a sample of patients with autistic spectrum disorder. **Method**: The charts of all patients with a diagnosis of autistic spectrum disorder, receiving care for psychomotor agitation and/or aggressive behavior in two psychiatric outpatient departments between 2001 and 2006, were reviewed. The Clinical Global Impression-Severity and –Improvement scales (CGI-S and CGI-I) were applied to the data retrieved from the charts. **Results**: The majority of the 26 patients included were treated with second-generation antipsychotics. A positive, statistically significant correlation was found between the implementation of pharmacotherapy and a reduction in CGI-S scores (p<0.05). Treatment response in patients with no mental retardation was better than in those mentally retarded (p<0.05). The majority of patients in whom clinical improvement was found following implementation of treatment had participated in at least one form of intervention therapy in addition to the principal treatment (p<0.05). **Conclusion**: Second-generation antipsychotics seem to reduce psychomotor agitation and aggressive behavior in patients with autistic spectrum disorder; however, further studies are required to evaluate the side effects of these drugs in relation to their beneficial effects.

KEY WORDS: antipsychotics, pharmacological, retrospective, autistic disorder, treatment.

Controle da agitação psicomotora e agressividade em pacientes com autismo: estudo retrospectivo de revisão de prontuário

Resumo – **Objetivo**: Avaliar a eficácia do tratamento farmacológico dos sintomas de agitação psicomotora e agressividade em amostra de pacientes com transtorno do espectro autista. **Método**: Foram revisados os prontuários de pacientes com diagnóstico de transtorno do espectro autista que procuraram atendimento por apresentarem agitação psicomotora e/ou heteroagressividade, atendidos entre 2001 e 2006, em dois ambulatórios de psiquiatria. Para avaliação da evolução dos pacientes aplicou-se às informações do prontuário a escala de Impressão Clínica Global Sintomas (ICG-S) e a Impressão Clínica Global Melhora (ICG-M). **Resultados**: A maioria dos 26 pacientes estava em tratamento com antipsicóticos de segunda geração. Houve correlação positiva e estatisticamente significativa entre a introdução do tratamento farmacológico e a redução nos escores da ICG-S (p<0,05). A evolução do tratamento farmacológico foi melhor para os pacientes sem retardo mental do que para aqueles com retardo mental (p<0,05). A maioria dos pacientes que obteve melhora clínica com o tratamento participava de ao menos uma intervenção auxiliar ao tratamento principal (p<0,05). **Conclusão**: Os antipsicóticos de segunda geração parecem reduzir a agitação psicomotora e agressividade em pacientes com transtorno do espectro autista no Brasil. É necessário que se avaliem os efeitos colaterais em relação aos efeitos benéficos dessas drogas.

PALAVRAS-CHAVE: antipsicóticos, farmacológico, retrospectivo, transtorno autista, tratamento.

---

[1]Undergraduate medical student, Bahia School of Medicine and Public Health (EBMSP), recipient of a research initiation grant from the Bahia Foundation for the Support of Science (FAPESB) # BOL1733/2006, Salvador BA, Brazil; [2]Professor of Pharmacology and Psychiatry, EBMSP, Salvador BA, Brazil; [3]Resident in Psychiatry, Teaching Hospital, Federal University of Bahia (UFBA), Salvador BA, Brazil. This study was developed with the support of the Bahia School of Medicine and Public Health, and received financial support from the Foundation for the Support of Research of the State of Bahia (FAPESB).

Dra. Camila Marinho Novaes – Rua Território do Guaporé 363 / 601 - 41830-520 Salvador BA - Brasil. E-mail: marinhocn@hotmail.com

Autism is a chronic disorder characterized by significantly impaired reciprocal social interaction and communication skills associated with restricted, repetitive and stereotyped behavior patterns and diminished focus of interests and activities[1]. It presents as a severe developmental abnormality, the symptoms of which first appear at some time between birth and the first 18 months of life[2]. Beside the children's difficulties, the dynamics of families of autistic patients generate difficulties to the emotional health of the group's members[3]. It is a disorder commonly associated with mental retardation, epilepsy and genetic complications, particularly fragile × syndrome[4]. Anatomical abnormalities are found in the majority of autistic patients examined with magnetic resonance imaging and SPECT[5]. Aggressive behavior is frequently seen in autistic spectrum disorder[6], and psychomotor agitation and aggressive behavior may represent negative prognostic factors[7].

The principal treatment of autism consists of the implementation of social skills training and educational measures. Pharmacotherapy may be required to control specific symptoms and behaviors in patients with more severe forms of the disorder for which habitual psychoeducational management is ineffective[8]. The classification of pharmacological therapy is based on drugs that, due to their neurochemical effect, supposedly act on key symptoms (pyridoxine, secretin and ocytocin) and on drugs used for the treatment of the behavioral disorders associated with autism (antidepressives, antipsychotic, psychostimulants and anticonvulsants)[8]. Antipsychotics, particularly haloperidol, are the most commonly used drugs for the treatment of behavioral disorders in patients with autistic spectrum disorder. Haloperidol has been found to be useful in reducing motor stereotypy, hyperactivity and mood changes, and promotes an improvement in social relationship skills[9,10] without resulting in excessive sedation[10,11]. An important limitation to the use of haloperidol in children is the possibility of the appearance of tardive dyskinesia, which may occur in up to 32% of cases[12,13]. The annual tardive dyskinesia incidence rates in children using second-generation antipsychotics were 0.35% and 2.98% in adults; while with first-generation antipsychotics was 7.7% in adults[13]. In four adult studies, however, tardive dyskinesia prevalence rates were 13.1% for second-generation antipsychotics, 15.6% for antipsychotic-free patients, and 32.4% for first-generation antipsychotics[13]. The use of second-generation antipsychotics has been recommended, since these drugs induce fewer extrapyramidal effects[14] and are believed to be less frequently associated with tardive dyskinesia. The second-generation antipsychotics currently under investigation for the treatment of autism are: risperidone, olanzapine, ziprasidone, quetiapine and clozapine[8]. In a recent literature review 21 trials with twelve different medications to treat aggression in autistic patients were identified[15]. Only risperidone and methylphenidate demonstrate positive results that have been replicated across at least two placebo controlled studies[15].

The objective of the present study was to review the charts of a sample of Brazilian patients with autistic spectrum disorder receiving pharmacological treatment for symptoms of psychomotor agitation and/or aggressive behavior towards others.

METHOD

This is a cohort study that retrospectively evaluated the charts of patients with autistic spectrum disorder from the date of their last consultation. Patient records were reviewed in two mental healthcare institutes: an outpatient department belonging to a National Health Service teaching/healthcare institute and the outpatient department of a private healthcare institute. The former is linked to the Bahia School of Medicine and Public Health (EBMSP), a teaching institute associated with the Bahia Foundation for the Development of Science (FBDC). It opens twice weekly and closes during the school holidays. The service provides care for adults and children, and all patients are examined by one single psychiatrist, who is accompanied by fourth-year medical students. The second outpatient clinic is a private institute for adults and children in the same city. It is open five days a week and the patients are attended by the same psychiatrist responsible for the patients at the teaching/healthcare institute.

The review included patients receiving care between January 2001 and June 2006 at either clinic. All patients with a diagnosis of autistic spectrum disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)[1] and who were seeking care because of behavioral disturbances (psychomotor agitation and aggressive behavior towards others and/or self) were included in the study. The patient was considered to have psychomotor agitation when there were reports on the chart of motor restlessness and hyperactivity in the home and school/social environments. Aggressive behavior was defined as reports on the chart of various episodes of apparently unjustified aggressive behavior towards others and/or self-harming behavior such as constantly hitting head or limbs on objects, biting themselves and self-mutilation.

The investigators completed a clinical form in which the following data collected from the charts was recorded: sex, age, medications used prior to the last treatment, medication currently in use, duration of use of the last medication adopted, dosage of the last medication prescribed, concomitance of other forms of therapeutic management (school, psychotherapy, occupational therapy, hippotherapy or speech therapy) and the presence or absence of associated mental retardation. Patients were considered to be mentally retarded when they had a developmental quotient less than 75, according to Behavior Developmental Scale of Gesell and Amatruda[16]. All these children

had lack of sphincterial control, lack of progress at school and lack of communication skills (either verbal or non-verbal) or only rudimentary communication skills. The Clinical Global Impression (CGI) scale was used to assess the evolution of patients[17]. The CGI scale is an instrument that evaluates the general clinical status of the patient based on clinical examination and/or the description of clinical status reported in the patient's medical chart. In this study, the CGI was adapted to evaluate the symptoms of aggressive behavior and psychomotor agitation described above. The Clinical Global Impression of Severity of Illness (CGI-S) scale, which measures the severity of current symptoms, was applied to the data recorded for the patient at the first consultation prior to the implementation of pharmacological treatment and at the last consultation that took place after implementation of pharmacological treatment. The patient received a score of 0 if not evaluated or was rated according to the seven-point CGI-S scale as follows: 1: normal, not ill; 2: minimally ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; and 7: among the most extremely ill patients. The second scale applied was the Clinical Global Impression Improvement (CGI-I), which considers the symptoms of patients following implementation of the last pharmacological treatment compared to the symptoms recorded prior to implementation of this treatment. The patient received a score of 0 if not evaluated or was rated according to the seven-point CGI-I scale as follows: 1: very much improved; 2: much improved; 3: minimally improved; 4: unchanged; 5: minimally worse; 6: much worse; and 7: very much worse. All the charts were reviewed by the same physician who had attended the patients and who applied the CGI-S and CGI-I scales based on the data collected from the charts. Evaluation was made with respect to the last pharmacological treatment used by the patient in the service in which he/she was receiving care. For the purposes of analyses, the CGI-I was dichotomized and patients were considered to have improved when they obtained a score of 1 (very much improved) or 2 (much improved); those who had scores of 3, 4, 5, 6 or 7 were considered not to have improved.

The data were stored in a database using the Epi Info 2002 statistical software program. The statistical analyses were carried out using the SPSS statistical software program, version 9.0. Stratified analysis was performed on the data in order to evaluate whether the variables of age, presence of mental retardation, duration of treatment, medication currently in use, healthcare clinic at which the patient was receiving care, and association with other therapeutic interventions had any effect on the results of treatment.

Permission to gain access to the patients' charts was granted by the Internal Review Board of the Bahia Foundation for the Development of Science under approval # 62/2006 of 11/10/2006.

RESULTS

Twenty-six patients with a diagnosis of autistic disorder in accordance with DSM-IV criteria, and who were in treatment for symptoms of psychomotor agitation and/or aggressive behavior towards others were included in this study. Table 1 summarizes the characteristics of the patients in this sample. Mean age of patients was 12.4 years (range 4–21 years). Mean duration of pharmacological treatment was 17 months. The minimum period of time evaluated following introduction of the drug was 2 months and the maximum was 42 months. With respect to nonpharmacological interventions, 12 patients (46%) underwent at least one type of intervention, 7 (27%) were submitted to two or more different types of intervention and in another 7 individuals (27%) no intervention was implemented other than pharmacological treatment. All patients who were submitted to some type of additional intervention attended a special school, while 26% were being accompanied by a psychologist, 5% by a speech therapist and 5% were carrying out hippotherapy.

The CGI-S scale was applied to all the charts to compare the symptoms present prior to and following introduction of the last pharmacological treatment prescribed. The intervals of time between the first and final evaluations were different for each patient. In the first evaluation, carried out prior to initiation of the current treatment, 1 patient (4%) was classified as mildly ill (CGI=3), 6

Table 1. Summary of sociodemographic data.

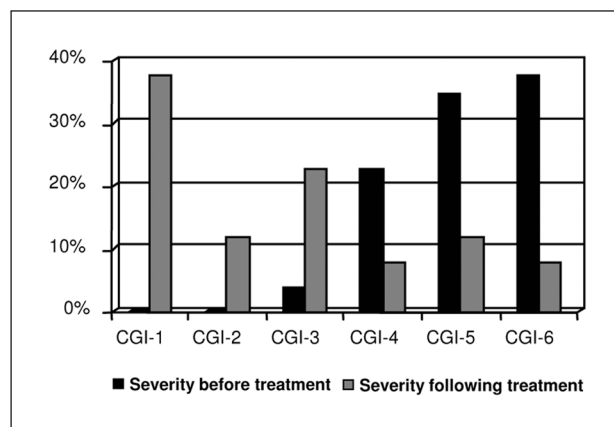| Characteristics	N	%
Males	23	88.5
>10 years of age	15	58
Mentally retarded	20	77
Patients attended at the private clinic	14	54
Duration of treatment ≥6 months	19	73
Submitted to nonpharmacological interventions	19	73

Figure. Correlation between improvement obtained and implementation of treatment.

Table 2. Variables associated with improvement following introduction of pharmacological treatment.

		Responded	Failed to Respond
Cognition*	Retarded	14 (70%)	6 (30%)
	Not retarded	6 (100 %)	0
Duration of treatment	More than 6 months of treatment	16 (90%)	3 (10%)
	Less than 6 months of treatment	4 (57%)	3 (43%)
Type of clinic	Private	11 (78%)	3 (22%)
	Public	9 (75%)	3 (25%)
Nonpharmacological interventions*	Yes	16 (80%)	3 (20%)
	No	4 (57%)	3 (43%)
Age	≤10 years old	9 (81%)	2 (19%)
	>10 years old	11 (73%)	4 (27%)

*$p<0.05$, Student's t-test.

patients (23%) as moderately ill (CGI=4), 9 (35%) as markedly ill (CGI-5) and ten (38%) were classified as severely ill (CGI=6). Following implementation of the last pharmacological treatment, clinical status was then classified as follows: 10 patients (38%) presented no aggressive behavior and/or psychomotor agitation (CGI=1), 3 patients (12%) were now classified as minimally ill (CGI=2); 6 patients were classified as mildly ill (CGI=3); 2 (8%) as moderately ill (CGI=4); 3 (12%) as markedly ill (CGI=5) and 2 (8%) as severely ill (CGI=6). Data analysis using Student's t-test showed a statistically significant change between the two results in CGI-S scores ($p<0.05$) (Figure).

When global improvement (CGI-I) was evaluated following implementation of the current treatment, 11 patients (42%) were very much improved, 9 (35%) much improved, and 1 patient (4%) was minimally improved. In five patients (19%), there was no clinical response to this therapy. No case was recorded of clinical deterioration following implementation of pharmacological treatment.

Table 2 summarizes the variables associated with improvement. Patients were considered to have improved when they had a CGI-I score of 1 or 2, i.e. very much or much improved, respectively. The response to pharmacological treatment was better in patients with no mental retardation than in mentally retarded patients ($p<0.05$). Of the 20 individuals in whom mental retardation was associated with autism, 5 (30%) failed to respond to treatment, whereas in the 6 individuals with no mental retardation, all patients responded to treatment. With respect to the duration of treatment, the difference between the groups was not statistically significant. In the group that had used the medication for less than 6 months, two patients were classified as severely ill, whereas in the group that had used the medication for more than 6 months, no patients were classified as severely ill (CGI=6); however, this difference was not statistically significant. No statistically significant difference was found between the pa-

tients who were receiving care at the private clinic and those attending the university healthcare clinic. Evaluation of the role of other nonpharmacological interventions showed that of the 20 individuals in whom clinical improvement was recorded, 16 (80%) had undergone at least one intervention in addition to the principal treatment, while only 4 patients (20%) who had not undergone any additional therapy responded to treatment ($p<0.05$). Analysis revealed no statistically significant difference in improvement in the patients as a function of age, improvement rates being around 75% both for the group of children >10 years of age and for the younger patients.

The medication used by the patients was divided into first and second-generation antipsychotics, the first-generation antipsychotics consisting of chlorpromazine, levomepromazine, thioridazine, trifluoperazine and zuclopenthixol; while risperidone, olanzapine, aripiprazole and quetiapine comprised the second-generation antipsychotics. Eighteen patients (69%) were using risperidone alone or in association with first-generation psychotics, and 13 of these patients (50%) were using risperidone as monotherapy. Four patients (15%) were using other second-generation antipsychotics exclusively, while 3 (12%) were using these medications in combination with first-generation antipsychotics. Only one patient (4%) was using a first-generation antipsychotic exclusively. Of the 18 patients using risperidone, 14 (78%) obtained what was considered a clinical improvement, while one had a minimal improvement in symptoms and in 3 patients there was no change in their clinical status. Of the 7 patients who used other second-generation antipsychotics, associated or not with first-generation drugs, a clinical improvement was found in 5 (71%); however, the difference between the groups was not statistically significant. Of the patients who failed to respond to the second-generation antipsychotics, 50% had been using the medication for less than six months.

DISCUSSION

Autistic spectrum disorder is a complex developmental disorder with multiple etiologies and varying degrees of severity[18]. Up to the present time, no definitive cure has been found for this disorder, and social and educational interventions are known to constitute the principal therapeutic measures used, while pharmacotherapy is used to help control specific symptoms and behaviors[8]. Drugs that improve associated symptoms such as psychomotor agitation and aggressive behavior towards others are of fundamental importance, since they allow the patients to take greater advantage of social and educational interventions.

The objective of this study was to evaluate the efficacy of pharmacological treatment on the symptoms of psychomotor agitation and/or aggressive behavior towards others in a Brazilian sample of patients with autism. The use of antipsychotics was found to result in much or very much improvement in the symptoms of aggressive behavior and psychomotor agitation in 77% of the patients. Risperidone was the most frequently prescribed antipsychotic, and some degree of clinical improvement was found in 78% of patients using this drug. Of the patients who used second-generation antipsychotics alone or in combination with a first-generation antipsychotic, a clinical improvement was found in 71%. Only 4% of patients used first-generation antipsychotics exclusively. An important limitation of the present study is that the side effects of the medications used were not quantified, which did not permit evaluation of the risks involved in the use of antipsychotics in this study sample. This limitation is due to the fact that this is a retrospective study and the data was not uniformly available in the charts reviewed.

Antipsychotics, including haloperidol and risperidone, are drugs that have been extensively investigated for the control of symptoms in children and adolescents with a diagnosis of autism[19]. Second-generation antipsychotics are preferred, particularly for children, since they induce fewer extrapyramidal effects and may be less frequently associated with tardive dyskinesia. Studies have shown that risperidone is a well-tolerated drug that has positive effects on the behavioral disorders frequently associated with autistic spectrum disorder[20]. The short-term benefit of the use of risperidone for the control of severe symptoms, irritability and hyperactivity in pediatric autistic patients appears to have been well-established[21,22]. The continued use of risperidone beyond six months has also been shown to be effective, significant weight gain being considered the principal side effect, followed by anxiety, fatigue and somnolence[21]. Discontinuation of the use of risperidone after six months has been associated with a rapid return of dysfunctional and aggressive behavior in the majority of patients, indicating that this drug may require long-term use[23].

Other second-generation antipsychotics are also being investigated for use in autistic patients[24]. An open study with olanzapine, used for 12 weeks in 8 patients with pervasive developmental disorders, 5 of whom were autistic, resulted in improvement according to the CGI-S scale in 6 of the 7 patients who completed the study[25]. The mean dose of the drug used was 7.8±4.7 mg/day and the side effects observed consisted of increased appetite and weight gain in all participants and excessive sedation in three patients. A study using ziprasidone for the treatment of 12 patients diagnosed with autistic spectrum disorder suggested that the drug has the potential to control symptoms of aggressive behavior, agitation and irritability in children, adolescents and young adults with autistic spectrum disorder. According to the CGI scale, six of the 12 patients (50%) were considered "much improved" or "very much improved". No significant weight increase was observed during this 6-week study[26]. Quetiapine was used in an open study in 6 male patients with autistic spectrum disorder and a mean age of 10.9±3.3 years for a period of 16 weeks. No statistically significant improvement was recorded at 16 weeks. Only 2 participants completed the study and were considered responsive according to the CGI scale. Three patients failed to adhere to treatment due to a lack of response and excessive sedation, which eliminated the possibility of increasing dosage. One patient had a probable convulsive crisis in the fourth week and also discontinued the study. Agitation, increased appetite and weight gain were the principal side effects[27].

In the present study, the combination of mental retardation and autism was found to be an important factor associated with poorer treatment outcome. The majority of patients included in this study, in which the sample consisted of patients who had sought outpatient treatment for psychomotor agitation and/or aggressive behavior towards others, were mentally retarded (77% of the sample). These data are in agreement with the literature, since patients with autistic spectrum disorder and mental retardation, who are aggressive towards others and/or self, comprise the most common psychiatric emergencies registered for this disorder[28]. Moreover, aggressive behavior is a common symptom in mentally retarded patients[29,30]. The proportion of patients who responded to pharmacological treatment was significantly greater among the patients who were not mentally retarded (100%) compared to those with mental retardation (75%). Other investigators have reported that patients with autistic spectrum disorder, mental retardation and aggressive behavior are more resistant to pharmacotherapeutic interventions[31].

Significantly more patients responded to pharmacological treatment in the subgroup submitted to concomitant nonpharmacological interventions (81%) compared to those who did not undergo these therapeutic measures (19%). Behavioral and educational interventions may increase the adaptive skills of the patients and promote better communication skills in patients with varying degrees of the disorder[7]. Controlled studies are being carried out that suggest an improvement in behavior following psychosocial therapy[32]. It should also be considered, however, that the children who do not participate in psychoeducational activities may be those with the most severe behavioral disorders, who for this very reason are less likely to respond to pharmacological treatment.

The present study has some methodological limitations. It is a retrospective study with no control group that uses a fairly nonspecific scale that was applied by the same clinician who treated the patients. In addition, the side effects of the medications used were not analyzed. Despite these limitations, this study is useful since clinical studies on patients with autistic spectrum disorder are sparse in our midst. In conclusion, pharmacological intervention with second-generation antipsychotics seems to be useful for the control of behavioral disorders such as psychomotor agitation and aggressive behavior in this Brazilian sample of patients with autistic spectrum disorder. Attending physicians should be alert, however, to the short- and mid-term side effects of the use of these drugs.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 2000.
2. Rapin I. Autistic children: diagnosis and clinical features. Pediatrics 1991;87:751-760.
3. Sprovieri MHS, Assumpção FB Jr. Dinâmica familiar de crianças autistas. Arq Neuropsiquiatr 2001;59:230-237.
4. Olley JG, Gutentag SS. Autism: historical overview, definition and characteristics. In: Jager DB (Ed.). Autism: identification, education and treatment. 2nd Ed. New Jersey: Lawrence Erlbaum Associate Publishers, 1999.
5. Machado MG, Oliveira HA, Cipolotti R, et al. Anatomical and functional abnormalities of central nervous system in autistic disorder: a MRI and SPECT study. Arq Neuropsiquiatr 2003;61:957-961.
6. Weller EB, Rowan A, Elia J, Weller RA. Aggressive behavior in patients with attention-deficit/hyperactivity disorder, conduct disorder, and pervasive developmental disorders. Psychiatry De J Clin 1999;60(Suppl): S5-S11.
7. Korkmaz B. Infantile autism: adult outcome. Semin Clin Neuropsychiatry 2000;5:164-170.
8. Moura AMR, Menezes APA, Pondé MP. Atualização na farmacoterapia do autismo. In: Garcia R, Pondé MP, Lima MG (Eds.). Atualização em psicoses. São Paulo: Phoenix, 2004:235-244.
9. Campbell M, Anderson LT, Meier M, et al. A comparison of haloperidol and behavior therapy and their interaction in autistic children. J Am Acad Child Adolesc Psychiatry 1978;17:640-655.
10. Anderson LT, Campbell M, Grega DM, Perry R, Small AM, Green WH. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984;141:1195-1202.
11. Anderson LT, Campbell M, Adams P, Small AM, Perry R, Shell J. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989;19:227-239.
12. Campbell M, Armenteros JL, Malone RP, Adams PB, Eiesenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. J Am Acad Child Adolesc Psychiatry 1997;36:835-843.
13. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 2008;21:151-156.
14. Findling RL, Schulz SC, Reed MD, Blumer JL. The antipsychotics: a pediatric perspective. Pediatr Clin North Am 1989;45:1205-1232.
15. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. J Child Adolesc Psychopharmacol 2008;18:157-178.
16. Gesell A, Amatruda. Diagnóstico do desenvolvimento: avaliação e tratamento do desenvolvimento neuropsicológico do lactente e da criança pequena, o normal e o patológico. Ed. 3. São Paulo: Atheneu, 2000.
17. Guy W . ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare. Washington DC: Publication ADM, 1976:534-537.
18. Rutter M, Schopler E. Classification of pervasive developmental disorders: some concepts and practical considerations. J Autism Dev Disord 1992;22:459-482.
19. Malone RP, Gratz SS, Delaney MA, Hyman SB. Advances in drug treatments for children and adolescents with autism and other pervasive developmental disorders. CNS Drugs 2005;19:923.
20. Chavez B, Chavez-Brown M, Rey JA. Role of risperidone in children with autism spectrum disorder. Ann Pharmacother 2006;40:909-916.
21. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. J Am Acad Child Adolesc Psychiatry 2005;44:1137.
22. Mukaddes NM. Short-term efficacy and safety of risperidone in young children with autistic disorder (AD). World J Biol Psychiatry 2004;5: 211-214.
23. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005;162: 1361-1369.
24. Stachnik JM, Nunn-Thompson C. Use of atypical antipsychotics in the treatment of autistic disorder. Ann Pharmacother 2007;41:626-634.
25. Potenza MN, Holmes JP, Kanes SJ, McDougle CJ. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol 1999;19:37-44.
26. McDougle CJ. Case series: use of ziprasidone for maladaptive symptoms in youths with autism. J Am Acad Child Adolesc Psychiatry 2002;41:921-927.
27. Martin A, Koenig K, Scahill L, Bregman J. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9:99-107.
28. Hellings JA, Kelley LA, Gabrielli WF, Kilgore E, Shah P. Sertraline response in adults with mental retardation and autistic disorder. J Clin Psychiatry 1996;57:333-336.
29. Turgay A. Aggression and disruptive behavior disorders in children and adolescents. Expert Rev Neurother 2004;4:623-632.
30. Rocha AF, Leite CC, Rocha FT, et al. Mental retadation: a MRI study of 146 Brazilian children. Arq Neuropsiquiatr 2006;64:186-192.
31. Horrigan JP, Barnhill LJ. Risperidone and explosive aggressive autism. J Autism Dev Disord 1997;27:313-323.
32. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomised controlled treatment study suggesting effectiveness. J Child Psychol Psychiatry 2004;45:1420-1430.