Dopamine Antagonists Ameliorate the Dyskinesias, Aggression, and Inattention of Persons with Mental Retardation Referred to Psychiatric Clinics

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Abstract

Background: Although dopamine antagonists are often administered to people with mental retardation, the neuropsychiatric effects are controversial. Objective: To characterize the effect of dopamine antagonists on movements and behaviors of persons with mental retardation. Method: Dyskinesias and behavioral problems are assessed in nine people with mental retardation referred to psychiatric clinics, including five men treated with dopamine antagonists in a dosage range equivalent to 67 to 220 mg chlorpromazine, and two men and two women who receive no medication during the preceding three months. Results: The nonmedicated subjects have higher levels of akathisia, stereotypies, tics, and other dyskinesias and lower global adaptive functioning. Utilizing the Mann-Whitney Test, nonmedicated subjects have more tics ($P < .006$), attention deficit disorder ($P < .018$), and overt aggression ($P < .015$); however, the Bonferroni correction for multiple comparisons renders all results nonsignificant. Conclusions: Dopamine antagonists ameliorate the dyskinesias, aggression, and inattention of some persons with mental retardation and behavioral problems. However, beneficial effects of dopamine antagonists must be weighed against adverse effects including withdrawal and tardive dyskinesias.

Key Words: aggression, attention, dyskinesias, mental retardation, stereotypies, tics

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Introduction

The beneficial and adverse effects of dopamine antagonists for individuals with mental retardation presenting at psychiatric clinics remain a topic of controversy. While multiple surveys in several locations have documented that 20-51% of people with mental retardation and other developmental disabilities in the United States of America receive psychoactive medications (Brašic et al., 1997c; 2000b), the efficacy of those pharmacologic interventions is uncertain. Although the benefits of the administration of dopamine antagonists to people with developmental disabilities are not established, there is evidence that people with developmental disabilities are at risk for adverse effects, including tardive and withdrawal dyskinesias (Brašic and Bronson,

2001). Understanding the effects of dopamine antagonists on the movements and behaviors of people with developmental disabilities referred to psychiatric clinics can be facilitated by review of data about tardive dyskinesia in other psychiatric patients.

Tardive dyskinesia, particularly orofacial movements in association with negative symptoms, and cognitive impairments, may manifest brain damage (Perris et al., 1979) in individuals with schizophrenia (Manschreck, 1989; Manschreck et al., 1990; Sorokin et al., 1988; Waddington et al., 1987), bipolar disorder (Waddington et al., 1989), epilepsy (Youssef and Waddington, 1988), dementia (O'Keane and Dinan, 1991; Sweet et al., 1992; Ticehurst, 1990), and mental retardation (Gualtieri et al., 1986; Youssef and Waddington, 1988).

The emergence of tardive orofacial dyskinesia in psychiatric patients (Waddington et al., 1993) may be hastened by chronic treatment with neuroleptics (Jenner and Marsden, 1989. The hypothesis that a pre-existing neurodevelopmental syndrome (Jones and Murray, 1991) may be responsible for adventitious movements in schizophrenia is confirmed by surveys (Christensen et al., 1970; Edwards, 1970) that provide neurological and pathological evidence of brain damage among institutionalized patients with orofacial dyskinesia induced by neuroleptics, and is substantiated by the retrospective observation of verbally mediated learning deficits in psychiatric patients with tardive dyskinesia (Famuyiwa et al., 1979) and by the prospective observation of a high incidence of tardive dyskinesia in psychiatric patients with poor initial cognitive function (Struve and Willner, 1983; Waddington et al., 1990).

Additional anatomic and psychological deficits are associated with tardive dyskinesia. For example, shortened left caudate T_2 relaxation time consistent with atrophy is identified in some schizophrenic patients who developed tardive dyskinesia (Bartzokis et al., 1990; Caligiuri et al., 1989; Mukherjee et al., 1991; Wilson et al., 1984). Furthermore, poor performance on neuropsychological tests of frontal lobe function is associated with tardive dyskinesia in a group of chronic schizophrenic patients (Brown et al., 1992).

Nevertheless, evidence of anosognosia and affective symptoms in some individuals with tardive dyskinesia suggest that other regions of the brain are involved in tardive dyskinesia (Myslobodsky, 1986). The cognitive deficits in tardive dyskinesia may represent a form of subcortical dementia (Gilleard and Vaddadi, 1986) or frontal lobe dysfunction (Wade et al., 1988).

Additionally, limb-truncal dyskinesia has been described in terms of a pathophysiologically and functionally discernible topographic tardive dyskinesia subtype. Schizophrenics with limb-truncal dyskinesia have been shown to demonstrate greater attentional and other cognitive dysfunction (Paulsen et al., 1994) and more negative symptoms (Brown and White, 1992; Brown et al., 1992) than those with orofacial dyskinesia.

A group of eight subjects with mental retardation manifested orofacial dyskinesias and diffuse impairments in motor control. Orofacial dyskinesias, stereotypies, and tics were more severe in the four unmedicated subjects and less severe in the four subjects who had been treated with dopamine receptors antagonists (Barnett and Brašic, 1995).

Based on our earlier study of medicated and unmedicated subjects with mental retardation (Barnett and Brašic, 1995) and the evidence for a predisposition to movement disorders and cerebral dysfunction in people with mental disorders excluding mental retardation, we hypothesize that some individuals with mental retardation possess an innate vulnerability to exhibit movement and behavioral disorders that is alleviated by dopamine antagonists. By expanding and refining our original sample, we seek to compare and contrast the dyskinesias, general social adjustment, and comorbid behavior disorders in two groups of individuals with mental retardation, one treated with neuroleptic medication and the other non-medicated (Brašic et al., 1998c).

Methods

Subjects

For three years subjects are recruited for this study from an urban psychiatric clinic for adults with mental retardation at a state developmental disabilities office and from a developmental disabilities clinic serving children, adolescents, and adults in the psychiatric department of a tertiary-care municipal hospital. The building that housed the psychiatric clinic at the state developmental disabilities office was an intermediate care facility (ICF) for approximately 200 people with mental retardation (MR) during the initial years of the study. The ICF closed during the course of the study resulting in placement of all the residents of the ICF in community residences, other institutions, or other settings during the course of the study. The psychiatric clinic continued to operate while the building was renovated from residential units to offices. Most of the patients referred to the psychiatric clinic in the state developmental disabilities office were adults. Because of the specialized services offered at the psychiatry clinic in the state developmental disabilities office, some patients were referred from other neighboring regions for consultation. However, most of the patients attending the psychiatric clinic at the state developmental disabilities office had originally resided at the ICF for people with MR. The developmental disabilities clinic in the psychiatric department of the municipal hospital offered highly specialized services resulting in referrals from neighboring states. Most of the patients in the developmental disabilities clinic in the municipal hospital were children. In both clinics subjects were referred by clinicians, including psychologists and pediatricians, who identified

emotional and behavioral problems, including depression and aggression, in need of specialized psychiatric consultation for diagnosis and treatment.

All adolescents and adults who registered in both clinics were eligible for this study. Head trauma resulting in loss of consciousness led to exclusion. In order to be included in the study, subjects were required to complete both the clinic evaluation, a process involving several clinic visits, and an additional neuropsychological evaluation (Barnett and Brašic, 1995; Barnett et al., 1998) requiring at least one additional two-hour session. Since the neuropsychological evaluation required the spoken responses of the subjects, all subjects for this study were verbal adults who cooperated with the neuropsychologist to complete the full neuropsychological battery. The results of the neuropsychological assessments will be published separately.

The subjects are nine adults who fulfilled contemporary criteria for mild or moderate mental retardation (American Psychiatric Association, 1994). In order to enlarge the original sample, one medicated man and one unmedicated man were added to the study. In order to eliminate atypical cases, we omitted the only adolescent, a girl, from the original group (Barnett and Brašic, 1995).

The subjects include five men (mean $\pm$ standard deviation (SD) age=33 $\pm$ 10; intelligence quotient (IQ) = 60 $\pm$ 7) treated with dopamine antagonists in a dosage range equivalent to 67 to 220 mg chlorpromazine and two men and two women with mental retardation (age=29 $\pm$ 7; IQ = 60 $\pm$ 4) who received no medication during the three months preceding evaluation except for one person who received a single dose of amitriptyline during the month before the evaluation. The five medicated subjects received neuroleptics for at least three months; one additionally received lithium carbonate. The non-medicated subjects had received thioridazine and/or benzodiazepines for less than a month over the year preceding the evaluation.

Adventitious movements, including akathisia, stereotypies, tics, and other dyskinesias, are rated independently in person by a neuropsychologist and three psychiatrists in a nonblind manner. To assess movements, the raters observe the subjects following the protocols of the Abnormal Involuntary Movement Scale (AIMS) (Brašic and Bronson, 2001; Guy, 1976), the Hillside Akathisia Scale (HAS) (Brašic and Bronson, 2001; Fleischhacker et al., 1989), and the Timed Stereotypies Rating Scale (TSRS) (Brašic and Bronson, 2001; Campbell, 1985). Subjects are rated on the basis of the observed clinical rating session lasting approximately 30 minutes. Subjects are rated solely on the basis of their performance in the assessment period. Due to the inability of the subjects and their caregivers to provide accurate historical data, no interview about past functioning is attempted for this study. The administration of rating instruments is modified to omit the clinical interview to elicit information about current and past movements and behavior that is part of the assessment protocol for several instruments utilized (Leckman et al., 1988, 1989; Simpson et al., 1979). Therefore, all assessments are based solely on the observed behavior of the subject during the clinical assessment session. Thus, the administration of several instruments is modified to match the capabilities of patients with severe cognitive limitations by omitting an interview of subject and family to determine current and past functioning (Barnett and Brašic, 1995; Brašic, 2000, 2001a, b; Brašic and Barnett, 1997; Brašic and Gianutsos, 2000; Brašic et al., 1994, 1996, 1997a,b, 1998a,b, c, 1999, 2000a,c). General dyskinesias are assessed using the Abnormal Involuntary Movement Scale (AIMS) (Brašic and Bronson, 2001; Guy, 1976) and the Tardive Dyskinesia Rating Scale (TDRS) (Simpson et al., 1979). Akathisia is evaluated with the Hillside Akathisia Scale (HAS) (Brašic and Bronson, 2001; Fleischhacker et al., 1989) and the Rating Scale for Drug-Induced Akathisia (RSDIA) (Barnes, 1989). Stereotypies are assessed with the Timed Stereotypies Rating Scale (TSRS) (Brašic and Bronson, 2001; Campbell, 1985). Tics are evaluated utilizing the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and the Clinical Global Impressions Scale for Tourette's Syndrome (CGISTS) (Leckman et al., 1988). Obsessions and compulsions are assessed by the Clinical Global Impressions Scale for Obsessive-Compulsive Disorder (CGISOCD) (Leckman et al., 1988). Attentional problems are evaluated by the Clinical Global Impressions Scale for Attention Deficit Disorder (CGISADD) (Leckman et al., 1988). Aggression is assessed with the Modified Overt Aggression Scale (MOAS) (Kay et al., 1988). Overall adaptive functioning is assessed utilizing the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983, 1985).

Statistical Analysis

The Chi-Square, Mann-Whitney, and Sign Tests were performed for between-group comparisons of independent samples. Pearson's Product Moment Correlation was utilized to assess the strength of association (Conover, 1980).

Results

Demographic and personal characteristics

Utilizing the Chi-Square (χ^2) Test for differences in probabilities (Conover, 1980), there are no significant differences in gender (χ^2= 0.287, 1 df, P = 0.750) and handedness (χ^2 = 0.032, 1 df, P = 0.750) between the medicated and non-medicated groups. Utilizing the Mann-Whitney Test (Conover, 1980), there are no significant differences in age (Mann Whitney Test Statistic = 0.137, P =0.555)

and intelligence quotient (Mann Whitney Test Statistic = 0, P = 0.500) between the medicated and non-medicated groups.

Behavioral assessment

Overall adaptive functioning is impaired in both groups equally on the CGAS (Shaffer et al., 1983, 1985), the CGISADD (Leckman et al., 1988), and the CGISOCD (Leckman et al., 1988) in both medicated and nonmedicated subjects. Behavioral assessments do not discriminate medicated and non-medicated groups.

Abnormal movements

Orofacial dyskinesia is diagnosed by a rating of 2 or higher on any one of the AIMS (Brašic and Bronson, 2001; Guy, 1976) items concerning the mouth and face. Three (75%) of the four nonmedicated subjects and three (60%) of the five medicated subjects exhibit orofacial dyskinesias utilizing the AIMS (Brašic and Bronson, 2001; Guy, 1976). Limb-truncal dyskinesia is diagnosed by a rating of 2 or higher on any of the AIMS (Brašic and Bronson, 2001; Guy, 1976) items concerning the limbs and trunk. One (25%) of the four nonmedicated subjects and one (20%) of the five medicated subjects exhibit limbtruncal dyskinesias on the AIMS (Brašic and Bronson, 2001; Guy, 1976). Overall tardive dyskinesia is diagnosed by any rating of 2 or higher on any item of the AIMS concerning the mouth, face, limbs or trunk (Brašic and Bronson, 2001; Guy, 1976).

Limb-truncal dyskinesia ratings are obtained from the mean scores of the extremity and trunk items of the AIMS (Brašic and Bronson, 2001; Guy, 1976).

In particular, orofacial dyskinesias are more prominent than limbtruncal dyskinesias in the nonmedicated subjects utilizing the AIMS (Brašic and Bronson, 2001; Guy, 1976) (Pearson's Product Moment Correlation r = 0.0356) (Conover, 1980). However, this finding is not confirmed utilizing the Sign Test (Conover, 1980) to test if the orofacial scores are higher then limbtruncal scores of the AIMS (Brašic and Bronson, 2001; Guy, 1976), TSRS (Brašic and Bronson, 2001; Campbell, 1985), and TDRS (Simpson et al., 1979).

Table 1. Probability Values by the Mann-Whitney Test (Conover, 1980) that Scores on the Abnormal Involuntary Movement Scale (AIMS) (Brašic and Bronson, 2001;Guy, 1976) Are Higher in Four Adults with Mental Retardation Referred to Psychiatric Clinics and Treated without Neuroleptics than in Five Adults with Mental Retardation Referred to Psychiatric Clinics and Treated with Neuroleptics

AIMS Category	Mann-Whitney Test Statistic	Probability Value
Orofacial	1.112	0.134
Limb-truncal	1.572	0.058
Severity	1.414	0.079

Table 2. Probability Values by the Mann-Whitney Test (Conover, 1980) that Akathisia Scores on the Hillside Akathisia Scale (HAS) (Brašic and Bronson, 2001; Fleischhacker et al., 1989), the Rating Scale for Drug-Induced Akathisia (RSDIA) (Barnes, 1989), and the Rating Scale for Tardive Dyskinesia (RSTD) (Simpson et al, 1979) Are Greater in Four Adults with Mental Retardation and Behavioral Problems Treated without Neuroleptics than in Five Adults with Mental Retardation and Behavioral Problems Treated with Neuroleptics

Instrument	Mann-Whitney Test Statistic	Probability Value
HAS Objective	1.246	0.107
RSDIA Objective	1.549	0.061
RSTD Face	0.122	0.452
RSTD Neck and Trunk	0.615	0.271
RSTD Upper Extremity	0.371	0.356
RSTD Lower Extremity	0.997	0.150
RSTD Entire Body	0.884	0.189

Scores for general dyskinesias (Brašic and Bronson, 2001; Guy, 1976) (Table 1), akathisia (Barnes, 1989; Brašic and Bronson, 2001; Fleischhacker et al., 1989; Simpson et al., 1979) (Table 2), stereotypies (Brašic and Bronson, 2001; Campbell, 1985), tics (Leckman et al., 1988, 1989), attention deficit disorder (Leckman et al., 1988), obsessive compulsive disorder (Leckman et al., 1988), and aggression (Kay et al., 1988) were all greater in non-medicated patients. However, no significant differences were observed except for the following findings. Utilizing the Mann-Whitney Test, the nonmedicated subjects had higher scores than the medicated subjects on the CGISTS (Leckman et al, 1988) (Mann Whitney Test Statistic = 2.513, P < 0.006) (Conover, 1980), the CGISADD (Mann Whitney Test Statistic = 2.109, P < 0.018) (Conover, 1980) and the MOAS (Kay et al., 1988) (Mann Whitney Test Statistic = 2.196, P < 0.015) (Conover, 1980). However, if the Bonferroni criterion is employed to correct for multiple comparisons, all differences are attenuated to nonsignificance. Scores for overall adaptive functioning (Shaffer et al., 1983, 1985) were higher, but not significantly higher, utilizing the Mann-Whitney Test (Conover, 1980), for medicated patients; this is consistent with the other findings because a higher score on the CGAS (Shaffer et al., 1983,

1985) indicates better behavior while a higher score on all the other instruments indicates worse behavior.

Discussion

Five participants with mental retardation referred to psychiatric clinics and treated with neuroleptics were compared and contrasted with four participants with mental retardation referred to psychiatric clinics and treated without neuroleptics for at least three months. Based on unblinded assessments using previously published rating scales, the neuroleptic-treated participants demonstrated less akathisia, stereotypies, tics, attention deficit, and aggression.

In this retrospective study, the prevalence of orofacial dyskinesia (60-75%) in this sample of young adults with mental retardation exceeds the range of the prevalence of orofacial dyskinesia (17% to 34%) previously reported in neuroleptic-exposed populations of individuals with developmental disabilities under 60 years of age (Cohen et al., 1991; Gualtieri et al., 1986; Youssef and Waddington, 1988). Additionally, idiopathic orofacial dyskinesia was significantly worse than limb-truncal dyskinesia in 75% of subjects with mental retardation either never exposed or exposed to a low dose for a short time. This prevalence is comparable to that in senile dementia (O'Keane and Dinan, 1991) and Down syndrome (Dinan and Golden, 1990; Kohen and Mathew, 1990). These findings suggest that some people with mental retardation may exhibit a vulnerability to dyskinesia, particularly orofacial dyskinesia. People with mental retardation may be vulnerable to develop dyskinesias, particularly orofacial, in response to a variety of trauma, including exposure to and/or withdrawal from dopamine antagonists. Since some participants in the nonmedicated group had previously received neuroleptics, although not in the three months preceding the study, some observed dyskinesias may represent tardive dyskinesias secondary to prior administration of the dopamine receptor blocking drugs (Brašic and Bronson, 2001). The medicated subjects may have manifested fewer dyskinesias due to a salutatory effect of the neuroleptics. Administration of neuroleptics may prevent the dyskinesias by blocking post-synaptic dopamine receptors. Long-term administration of neuroleptics, however, may lead to upregulation of the post-synaptic dopamine receptors and supersensitization to dopamine resulting in further dyskinesias. While administration of neuroleptics may suppress dyskinesias in people with mental retardation, the beneficial effect must be balanced against adverse effects including the development of severe permanent withdrawal and tardive dyskinesias.

Non-medicated patients manifested more aggression, attention deficit, and tics than the medicated patients. Thus, we conclude that dopamine receptor antagonists may provide protection against these behavioral and movement disorders in some persons with mental retardation. These results suggest that dysregulation of central dopamine may contribute to aggression, lack of attention, and tics in persons with mental retardation. While acute benefits are likely to result when people with mental retardation are given dopamine receptors antagonists, long-term treatment may result in the development of intractable movement disorders, including withdrawal and tardive dyskinesias (Brašic and Bronson, 2001). An alternative explanation is that the medicated sample had fewer problems with aggression, attention deficits, and tics than the non-medicated group at baseline.

The several limitations of this study must be addressed in order to put the findings in the context of the published literature. This was a retrospective study so it is not known whether the treated and untreated patients had comparable levels of movements, attention deficit, and aggression before treatment with neuroleptics. Also non-medicated subjects in this study had received prior treatment with thioridazine and benzodiazepines, although not in the three months preceding the assessment. Thus, the baseline ratings of the non-medicated subjects before they ever received psychoactive medications are unknown. Therefore, non-medicated subjects may have manifested neuropsychiatric effects of earlier treatment with psychoactive medications. It is unknown if the medicated and non-medicated subjects in this study had comparable levels of neuropsycyhiatric conditions, including dyskinesias and aggression, initially before ever receiving medication; the medicated participants may actually have fewer disturbances including dyskinesias and aggression originally. Another limitation to the study is the use of scales suitable to assess specific movement disorders, e. g., akathisia (Barnes, 1989; Brašic and Bronson, 2001; Fleischhacker et al., 1989), stereotypies (Brašic and Bronson, 2001; Campbell, 1985), and tics (Leckman et al., 1988, 1989). The scales do not distinguish different movements in the same patient. Distinguishing among types of movement required clinical judgment. Future studies of larger sample sizes of subjects with only single movement disorders would help to clarify the presence of movements and behavioral phenomena in those groups.

The subjects represent those adults with mental retardation attending psychiatric clinics for those with developmental disabilities who completed the extensive neuropsychological testing battery in additional to the complete clinical evaluation. Therefore, the findings need confirmation through prospective studies with larger samples at multiple centers. A preferable design for future studies is the assessment of blinded videotapes of the same groups of subjects before and after specific durations of treatment with specific neuroleptics. Future studies to confirm the findings with medicated subjects and never medicated subjects are needed. Additionally visualization of neurotransmitters in the brains of subjects before and during treatment with medications is needed to clarify the effects of the interventions. The neuroimaging protocols that identify deficits in other neuropsychiatric disorders (Brašic and

Wong, 2001; Wong and Brašic, 2001) are being applied to mental retardation and other developmental disabilities to clarify the disturbances in neurotransmitter pathways..

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