sample of the child (t = 6 hours after dose). The milk samples were obtained by expressing the milk shortly before breast-feeding (Fig. 1).

Risperidone and 9-hydroxyrisperidone levels in plasma and breast milk were quantified by high-performance liquid chromatography. Risperidone could be detected in the serum of the mother and its active metabolite in the breast milk, but no risperidone could be detected in the serum of the baby. The milk-to-plasma ratio for 9-OH-risperidone was calculated from the area under the concentration-time curve. The calculated ratio was 0.88. The milk-to-plasma ratio for risperidone could not be calculated, because all risperidone in milk samples was below the detection level of our assay. Hill et al. found ratios of 0.42 (risperidone) and 0.24 (9-OH-risperidone). The apparent greater excretion in milk that we found is probably an overestimation because measured milk and serum levels were just above the detection level of the assay (the lower the concentration, the bigger the chance of a bias due to limitations of the analytical assay).

The exposure of the baby to the drug and its metabolite was calculated as the product of the average drug concentration in breast milk and a milk intake of 150 mL/kg per day. We found that the oral intake of 9-OH-risperidone by the baby was 4.7% of the weight-adjusted oral intake of the mother. Because risperidone samples in milk were all below the detection level, we could not calculate the risperidone exposure through breast-feeding. Hill et al. found exposure levels of 0.46% (9-OH-risperidone) and 0.84% (risperidone).

**DISCUSSION**

In accordance with other studies, we found that the active metabolite of risperidone, 9-OH-risperidone, can be detected in breast milk. Risperidone and its active metabolite, 9-OH-risperidone, are both active drugs. The concentration is, as described in other studies, less than the 10% level of concern recommended for safe breast-feeding with many drugs.

We aimed to collect the milk samples out of a full expression feeding to avoid a concentration bias in the foremilk or hindmilk, but in practice this appeared impossible for the mother. When the child started to cry, the mother could not resist comforting her child with breast-feeding. Aichhorn et al. found no significant difference in concentration of risperidone and its active metabolite in foremilk or hindmilk. Presumably, this is no important bias in our study. In the serum sample of the child, no risperidone or 9-OH-risperidone was detected. This finding suggests that a low-dose risperidone does not accumulate in newborns. When this study was performed, the baby was 3 months old. Risperidone and its active metabolite are both metabolized by CYP450 liver enzymes. Each individual isofrom of phases I and II enzymes has unique developmental profiles. In vitro data show the presence of significant amounts and activity of phases I and II enzymes at 2 months of age. A study on the pharmacokinetic data of 40 drugs in children of different age groups showed that the mean elimination half-life of these substrates approached adult levels at 2 months of life. At 6 months, the mean elimination half-life of most substrates approaches adult levels. In vitro data suggest that although liver enzymes in general have not matured fully, a significant amount and activity of enzymes are present at this age.

Regarding this, it is possible that the concentrations of risperidone and its active metabolite might have been higher when the baby was younger, but at the time the test was done, the baby should have been able to metabolize the medication as adult people do. For women with a preexisting psychiatric illness, specifically with a bipolar disorder, the risk of deteriorating in the postnatal period is as high as 40% to 70%. With drug therapy, this rate is reduced to 10%.

A couple of earlier published reports on the use of risperidone during lactation failed to observe any adverse effects in infants. In our study, no abnormalities were found either. Taking into account the detected concentrations of 9-OH-risperidone in mother's milk and child serum, we conclude that (1) there seems to be no significant hazard for the breast-fed infant in the short term when low doses are used; (2) the best way to estimate the drug exposure to the child is to measure the concentration in the child serum in the steady state; (3) long-term follow-up studies are warranted; and (4) clinical observation after birth for signs of withdrawal is still mandatory.

The decision to breast-feed or not remains an individual one. The mother should be provided with appropriate information about the risks and the benefits for both mother and child. With this study, we hope to add further information. Hopefully, over time, enough data are gathered to give experience-based recommendations to mothers who use risperidone and desire to breast-feed their infant.

**AUTHOR DISCLOSURE INFORMATION**

The authors have no financial interests to declare.

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**Risperidone Reduces Tic-Like Motor Behaviors and Linguistic Dysfluencies in Severe Persistent Developmental Stuttering**

To the Editors:

Developmental stuttering is characterized by tonic-clonic, tic-like motor...
behaviors of the orofacial district, which result in a disorder in the rhythm and
fluency parameters of voluntary speech. Developmental stuttering has a childhood
onset rate of almost 5% in the typically developing population; yet, it is unclear
why in about 1% it persists into adulthood, determining a severe communication
impairment. Neuroradiology data suggest a disorder in cortico-subcortical networks
subserving speech selection, initiation, and timely execution in developmental
stutterers, thus supporting neuropsychological models that posit a joint contribu-
tion of disordered linguistic and motor systems in defining the type and fre-
cuency of stuttering behaviors. Furthermore, it has been shown that, contrary to
fluent controls, persistent developmental stutterers activate neocortical left hemi-
spheric speech areas before supramodal frontocentral ones involved in executive
programming. It follows that a core deficit in the ordered, timed execution of
sequence patterns of speech segments might act as a neuropsychological deter-
mnant of the persistence of stuttering behaviors into adulthood.

The dopaminergic activity of the basal ganglia has been involved in non-
motor functions such as sequencing, neural timing, time discrimination, and perception/
expression of auditory/language units, as well as in the selection, initiation, and
execution of actions. Positron emission tomography findings uphold a key influence
of dopaminergic activity on stuttering by showing a marked increase in dopaminergic
afferent activity in the tail of the left caudate nucleus in stutterers compared with healthy controls. Such
increase is thought to translate into a persistent hypereactivation of the structure
and its neocortical network (left insula, superior and ventromedial left tempo-
ral areas). Neuropsychopharmacological evidence points to a key role for dopamine-
regulated neural networks also in psychiatric disorders that share a behavioral
blueprint with developmental stuttering.

Risperidone is an atypical antipsychotic drug that acts as a D2 and 5-HT2A antago-
nist, with a low incidence of extrapyramidal symptoms and tardive dyskinesia.
It is used in the treatment of neurodevelop
damental disorders characterized among
other things by involuntary, compulsory movements (pervasive developmental
disorders, attention-deficit/hyperactivity disorder, obsessive compulsive disorder,
and Tourette syndrome), and its efficacy in the treatment of stuttering has been also pro-
posed, although there exist reports of risperidone-induced stuttering in psychiatric
patients. Levomepromazine, an anti-
psychotic drug characterized by a 5:1 ratio
affinity to 5-HT2A/D2, has been shown to
induce stuttering in adults. This suggests
that stuttering behaviors may be causally linked to an imbalance between
dopaminergic and serotonergic activity.
Such a hypothesis would also explain the
different degrees of efficacy of selective
serotonin reuptake inhibitor drugs such as
paroxetine in controlling dysfluencies, particularly within the motor domain.
To further explore this issue, we exam-
ined both motor and linguistic aspects of
speech in a young adult male with
persistent developmental stuttering who underwent treatment with risperidone.

CASE REPORT

B.P. is a right-handed 24-year-old Italian man with a diagnosis of severe
persistent developmental stuttering (as defined by the Stuttering Severity Instru-
ment), resistant to behavioral treatment. No familial history of language disorders
was evidenced, and no major neurological deficit was detectable at routine exami-
nation. The research was approved by the Ethics Committee of the University of
Trieste and was run according to the
Declaration of Helsinki. B.P. volunteered
to a trial of risperidone and signed a
written informed consent. Before starting
treatment, he underwent an electrocardi-
ographic and a cardiological examina-
tion; hepatic, pancreatic, and hematologic
parameters were collected (baseline).
B.P. was commenced on risperi-
done in March 2004 and took 0.5 mg
of active drug every evening (first treatment)
for 6 weeks. At the end of this period,
baseline medical examinations were re-
peated, and a 6-week washout period was
determined (first washout). At the end
of this period, B.P. took again 0.5 mg
of active drug every evening for 6 weeks
(second treatment), followed by medical
examinations and a 12-week washout pe-
riod (second washout).

The electrocardiography and the
hepatic, pancreatic, and hematologic pa-
rameters were normal at baseline, and no
dramatic increase was evidenced through-
out the therapy, which was therefore com-
pleted in due course.

At the end of each of the 5 key
therapy periods (time variable = baseline,
first treatment, first washout, second

FIGURE 1. Percentage of stuttering behaviors sampled within each treatment period.

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structure to the variance-covariance matrix), the model resulted in a significant effect of time and stuttering on phrases for jaw movements (Table 1, upper half).

We then applied the same analysis to the linguistic classes. A significant change in time for stuttering on function words was evident (Table 1, bottom half). No significant change in time was found for both open-class words and phrases, although they also showed a decrease. Finally, we observed a relevant association between jaw movements and stuttering on function words, with 84.61% of jaw movements appearing within an utterance that also contained 1 or more episodes of stuttering on function words (odds ratio, 34.04; Fisher exact test for count data, P < 0.001).

**DISCUSSION**

B.P.'s speech was found to be significantly free from both major involuntary orofacial movements and linguistic stuttering after 2 consecutive 6-week treatment periods with risperidone, with intervals of a 6-week washout period and followed by a 12-week washout period to determine long-lasting effects. The dopamine-antagonist effect of risperidone might have acted by reducing the effect of dopaminergic projections on the left caudate nucleus, thereby enhancing its activity and improving control over voluntary speech and involuntary, tic-like movements of the orofacial district. However, statistical analyses allowed us to check for the overall effect of time only, irrespective of differences among the different treatment periods. Being based on a single-case study, our findings require replication of research procedures on larger samples.

We wish to point out that both motor and linguistic aspects of stuttering behaviors improved. The association between jaw blocks and stuttering on function words suggests that they co-occur to a significant extent within the same utterance. They may share a difficulty in the matching of the bisque sequence of oral movements necessary for uttering short-lasting function words and the underlying auditory sensory model,6 an effort load that might trigger the release of involuntary movements. As for the significant effect on jaw movements of stuttering on phrases, their characteristics of length and complexity may also have causal connections with respect to involuntary jaw movements.

Given the reversibility of its overall low extrapyramidal signs, risperidone may be indicated in cases of persistent developmental stuttering. However, the exact physiological mechanisms of its mode of action are still unclear. Some case reports suggest that treatment with atypical antipsychotics can induce stuttering.10,14,17 Generally, such cases have occurred in patients with previous exposure to different dopamine antagonists in relation to different psychiatric and brain pathological findings, but with no history of developmental stuttering. This could suggest the possibility of a "tardive" form of stuttering unmasked by risperidone treatment or represent a further hint at the importance of neurotransmitter balance for successful speech control. A progressive loss of D2 dopaminergic pathways in the basal ganglia, especially in the caudate nucleus, has been recently linked to age-related decline of dopamine-transporter density in the human brain due to a loss of substantia nigra cells.18 Speculatively, we suggest that developmental stuttering is more likely to become persistent when genetic factors determine an exceeding dopaminergic activity, for example, by reducing the normal rate of apoptosis of substantia nigra neurons,19 which in turn would prevent the gradual onset of age-related, regulatory processes in the nigrostriatal connections.

**ACKNOWLEDGMENTS**

The authors thank two anonymous reviewers for helping improving the overall quality of their case description.

**AUTHOR DISCLOSURE INFORMATION**

The authors have no conflicts of interest or disclosures to report.

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Aripiprazole-Associated Bruxism, Akathisia, and Parkinsonism in a Bipolar Patient

To the Editors:

Aripiprazole, a partial dopaminergic agonist, represents a well-tolerated and effective addition to the antipsychotic armamentarium. Trials have shown that rates of extrapyramidal side effects (EPSE) with aripiprazole are similar to those of placebo administration, although there are some case reports documenting aripiprazole-associated EPSE.2,3 However, to our knowledge, there are no literature data addressing aripiprazole-associated bruxism accompanied with parkinsonism and akathisia. Here, we report the case of a patient who developed bruxism, akathisia, and parkinsonism during treatment with lithium-aripiprazole combination and completely remitted after the withdrawal of aripiprazole.

CASE REPORT

A 20-year-old woman was admitted to our inpatient clinic. On examination, she was found to experience grandiosity, persecution and erotomanic delusions, accelerated association, aggressive behaviors, increased libido, psychomotor agitation, excitement, logorrhea, irritable mood and decreased need for sleep. She experienced these symptoms on most days and nearly every day during 2 weeks before admission. There was no personal history of substance abuse and no family history of mental illness. She was diagnosed with bipolar disorder (first episode, manic) based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision).

Initially, her Young Mani Rating Scale and Brief Psychiatric Rating Scale total scores were 27 and 24, respectively. Subsequently, aripiprazole was started at a dosage of 5 mg/d, which was titrated up to 15 mg/d in 2 weeks. Concomitantly, lithium carbonate was started at a dosage of 600 mg/d, which was gradually titrated up to 1200 mg/d. The mean plasma level of lithium was 0.82. The patient did not receive any oral or parenteral antipsychotic beside aripiprazole. On the third week after hospitalization, there was significant improvement of psychiatric symptoms. The patient's total scores on the Young Mani Rating Scale and Brief Psychiatric Rating Scale on the third week of admission were 4 and 3, respectively. However, after a week of treatment with aripiprazole (15 mg/d) and lithium carbonate (1200 mg/d), she developed bruxism of mixed types—both grinding and clenching. The teeth movements were so obvious that others could hear them easily. Her complaints included masseter tightness, headaches, and tooth pain. These involuntary movements were observed only while she was awake. They were regular and rhythmic and would disappear while eating and speaking.

On the next day, she had developed a severe manifestation of inner restlessness and anxiety associated with increased leg movements and body rocking. The patient's full physical, neurological, and laboratory examinations showed normal findings. The mean plasma level of lithium was 0.83. A brain magnetic resonance imaging and electroencephalogram revealed no abnormality in the brain. In addition, there was no personal or family history of movement disorder or other neurologic disorder. The patient was diagnosed as having bruxism accompanied with drug-associated akathisia. Her total score on the Barnes Akathisia Rating Scale (BARS) was 11.6 Subsequently, aripiprazole was reduced to 10 mg/d and lorazepam 2.5 mg/d (per os) was added to ongoing medication. After 3 days under this treatment, the patient noted partial improvement in her akathisia and bruxism. Her total score on the BARS was 8. Also, parkinsonism symptoms such as bilateral resting hand tremor, parkinsonian gait, bradykinesia, and rigidity were found in her clinical examination. Her Simpson-Angus Scale (SAS) score was 14.

Subsequently, biperiden, per os at a dose of 2 mg/d, was added to her treatment regimen, aripiprazole was reduced to 5 mg/d, and lorazepam was gradually stopped. On the fifth day of treatment with aripiprazole at 5 mg/d, biperiden at 2 mg/d, and lithium at 1200 mg/d, there was a significant improvement in her parkinsonism, bruxism, and akathisia symptoms. Her SAS and BARS scores were 6 and 5, respectively. It was decided to completely stop administration of aripiprazole. At the end of the first week after stopping the aripiprazole, we observed that her bruxism, parkinsonism, and akathisia symptoms had been completely resolved. Her SAS and BARS scores were 0 and 0, respectively. Subsequently, biperiden treatment was tapered and discontinued within 1 week. During the follow-up, after stopping aripiprazole and biperiden, there was