

# Treating Schizophrenia With the Diuretic Bumetanide: A Case Report

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**Abstract:** Administration of the diuretic and NKCC1 chloride cotransporter antagonist bumetanide reduces the severity of autism spectrum disorders in children, and this effect is mediated by a reduction of the elevated intracellular chloride concentrations and a reinforcement of GABAergic inhibition (Lemonnier et al *Transl Psychiatry*. 2012;2:e202; Tyzio et al *Science*. 2014;343:675–679). Here, we report that this treatment also reduces the severity of symptoms in an adolescent with schizophrenia. Long-term treatment reduced hallucinations significantly, suggesting that this treatment may also be useful to treat schizophrenia. Further clinical trials and experimental studies are warranted to test this hypothesis.

**Key Words:** schizophrenia, bumetanide, intracellular chloride, treatment, GABA

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Although controversial, links between schizophrenia and autism spectrum disorders (ASDs) have been repeatedly suggested, relying on clinical observations,<sup>1–3</sup> a possible similar genetic contribution to both disorders<sup>4–6</sup> and their neurodevelopmental origin.<sup>7–9</sup> Occasionally, schizophrenia and autistic disorders have been reported in the same family.<sup>10</sup> Studies of individuals with 22q11 deletion suggest increased risk for autism spectrum, schizophrenia spectrum, and other psychotic disorders,<sup>11,12</sup> and subplate region mutations are associated with autistic or schizophrenic manifestations.<sup>13</sup> Other suggestions, however, challenge the strong bond between autism and schizophrenia.<sup>14</sup>

Clinical developmental observations suggest similarities in both disorders. Thus, children with ASD sometimes evolve toward schizophrenia.<sup>15</sup> In a study on 18 teenagers who started schizophrenia precociously, 56% of the patients had symptoms compatible with an Asperger syndrome diagnosis (2 of them were given this diagnosis during childhood).<sup>16–18</sup> In the NIMH study, premorbid signs of schizophrenia include 55% with language, 57% with motor, and 55% with socialization disorders.<sup>19,20</sup> A similar fMRI pattern of activation by a social request has been reported in subjects with schizophrenia and Asperger syndrome.<sup>21,22</sup>

Valium and benzodiazepines often produce paradoxical responses in patients with autism, suggesting elevated intracellular chloride ([Cl]<sub>i</sub>) concentrations and excitatory actions of GABA.<sup>23</sup> Similar alterations have been observed in many pathological conditions, suggesting treatment based on reducing (Cl)<sub>i</sub> to reinstate GABAergic inhibition.<sup>24,25</sup> Relying on these observations, we have recently shown in a double-blind randomized study that the diuretic NKCC1 chloride importer antagonist bumetanide that reduces intracellular chloride also attenuates the severity of children with

ASD and adolescents with Asperger syndrome.<sup>26</sup> This treatment also ameliorated visual recognition of emotive figures and activation of brain regions involved in face recognition in adolescents with Asperger syndrome.<sup>27</sup> The concept underlying these clinical trials has now been validated in 2 animal models of autism showing elevated intracellular chloride concentrations and excitatory actions of GABA during birth.<sup>28</sup> Electrical and behavioral features are ameliorated by maternal administration of the diuretic before delivery.<sup>28</sup>

Because of the implicit similarities between schizophrenia and Asperger syndrome, we decided to test whether this rationale is also valid for schizophrenia. Indeed, although risperidone, often used to treat autism, exert positive effects on schizophrenia, social interactions are not ameliorated significantly by the treatment.<sup>29,30</sup> When subject have both Asperger syndrome and schizophrenia, antipsychotic agents do not improve global functioning of the subject.<sup>31</sup> Here, we report the case of a teenager for whom the bumetanide allowed an improvement in social interactions and an extinction of hallucinations after 1-year treatment.

## CLINICAL CASE

H. was born on July 23, 1996, the fourth and last child of his siblings. The pregnancy happened in an anxious climate for the mother who took carbamazepine due to secondary epilepsy. The delivery proceeded satisfactorily despite bradycardia. H. sat at 8 months and walked at 14 months. First words were said at 21 months, and first sentences were said at 27 months. Maternal familial history included an uncle that had schizophrenia and was treated by neuroleptic in a day care hospital.

In January 2002, H. is seen in a child psychiatry department and placed in a day care hospital. Clinicians noted that the patient has difficulties in acknowledging others, tendency to isolate, commitment into self-centered activities, difficulties to access symbolization, a limited and rigid imagination with crude and archaic themes, and monochromatic and colorless drawings but with good level language. During modeling clay activity, H. parceled the material and had difficulties to construct. Three half-day sessions per week in a day care hospital were continued until July 2003. In September 2003, he started elementary school along with psychotherapy.

His teacher noted the following from the patient: daydreaming, good reasoning, extensive vocabulary, formal language, and text creativity. During breaks, H. was often in a parallel world, walking like a robot (turning on himself, using his arms as machine guns); H. lashes out on the other children (kicks) and is easily irritated claiming that he cannot control himself. Integration is reported as being acceptable albeit the importance of boundaries. H. complains of ideas in his mind including monsters wanting to hurt him despite the absence of wounds; he was claiming that one of them did hurt him while sleeping. Initiated in November 2004, treatment with risperidone (1 mg/d, raised to 2 mg/d in February 2005) led in March 2005 to a more relaxed state of mind. In March 2007, a checkup is made including a BPRS (Brief Psychiatric Rating Scale),<sup>32</sup> a SANS (Scale for the Assessment of Negative Symptoms),<sup>33</sup> and a SAPS (Scale for the Assessment of the Positive Symptoms),<sup>34</sup> which gave the following results:

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- BPRS schizophrenia score, 32; depression score, 14; total, 46
- SANS affective flattening score, 16; alogia score, 10; avolition/apathy score, 4; anhedonia/asociality score, 7; attention score, 3
- SAPS hallucinations score, 6; delusions score, 4; bizarre behavior score, 2; positive formal thought disorder score, 10

In September 2008, despite continuous risperidone treatment and entering middle school, H. stressed that he is often in his world, needing that for self-fulfillment. Inspired by the Lord of the Ring, H. writes a novel on this world with maps of parallel worlds inhabited by elves, monsters, and other creatures, some were nice, some were aggressive. Because of persistent sleeping problems, H. receives in addition to risperidone, melatonin (4 mg) each night. He had difficulty in socialization; H. has no friend, and he is not interested to others. At this moment, we performed an ADI-R (Autism Diagnosis Interview, Revised)<sup>35</sup> with the parents. The scores are as follows:

- Reciprocal social interactions, 17 (cutoff, 10), especially difficulties to establish relationship with his peers (8/8), lack of shared pleasure (4/6)
- Language/communication, 16 (cutoff, 8), especially the items of nonverbal communication (12/14)
- Restricted, repetitive, and stereotyped behaviors and interests, 5 (cutoff, 3)
- Developmental abnormalities at or before the age of 36 months, 3 (cutoff, 1)

Because of the social difficulties, we decided to try a treatment with bumetanide that has just proven efficacious in treatment of socialization in autism.<sup>26</sup> In addition to risperidone and melatonin, H. received 2 mg bumetanide starting from November 2010. This treatment eased social interactions, participation in class, and communication with other students and facilitated family life. However, at consultations, H. keeps describing his own world with the same themes. In June 2011, H. stopped risperidone because of an 8-kg weight gain and remained with bumetanide and melatonin. Strikingly, in May 2012, 11 months after shifting to bumetanide, his internal world disappeared totally; he is more relaxed, he sleeps better, and schooling is easier, which was also attested by teachers and relatives. However, consequently to a disappearance of his internal world, H. decided to stop bumetanide treatment in June 2012. Two and a half months later, the hallucinations reappeared with enhanced severity leading him to return to bumetanide because "he was afraid of what was happening to him." In September, H. had a severe hallucination, requiring urgent treatment. We prescribed bumetanide and 2 mg of risperidone a day. The symptoms decreased rapidly, allowing schooling. In July 2013, H. stopped risperidone remaining only with bumetanide, and in October he said, "The symptoms are still present, but I can manage them and put them aside."

## DISCUSSION

Our observations suggest that bumetanide might have a positive effect on schizophrenia. Yet, there are several obvious caveats. First, the symptoms of H. are a mix between positive and negative symptoms of schizophrenia attested by BPRS, the SANS, and SAPS (filling the criteria of the *International Classification of Diseases, Tenth Revision* for this disorder).<sup>36</sup> Although not common, early signs of schizophrenia are attested in several studies.<sup>19,37</sup> Prodromal symptoms of schizophrenia include depressive mood, anhedonia, guilt and death ideas, mood swing, apathy, lack of vital strength, boredom and lack of interest, asthenia and lack of energy, attention and focus disorders, somatic complaints, weight loss and loss of appetite, sleep disorders, social behavior deterioration, impulsive, strange and aggressive behavior,

obsessive compulsive disorders, speech anomalies, the exacerbation of the interpersonal sensitivity, and suspicion; these are also commonly observed in autism and may lead to an autism diagnosis,<sup>38</sup> and it is not surprising that the ADI-R performed in 2010 includes autistic symptoms. The *International Classification of Diseases, Tenth Revision*<sup>36</sup> and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*<sup>39</sup> advise to exclude a patient with schizophrenia from autism diagnosis, as both diagnosis cannot be made on the same subject. Teenagers with schizotypal personality disorders have high scores at ADI-R.<sup>14,31,40</sup>

Second, this is an open case report that must be validated or confirmed by a double-blind trial.

However, extensive experimental observations are in accord with the working hypothesis. Anomalies of intracellular chloride levels and a shift of the polarity of GABA has been reported in a wide range of brain disorders, including epilepsies brain damage and spinal chord lesions<sup>24,25</sup> as well as autism and schizophrenia.<sup>41-47</sup> Paradoxical actions of GABA acting drugs such as benzodiazepines have been reported in autism,<sup>23</sup> raising the possibility that bumetanide might improve the symptoms by reinforcing GABAergic inhibition.<sup>24</sup> The long latency of bumetanide effects can be ascribed to a slow accumulation of the diuretic due to binding, absorption by albumin, and rapid degradation. The improvement is unlikely due to risperidone that was stopped 11 months earlier, and the reappearance of hallucinations 3 months after the bumetanide was stopped, as well as the lack of effects of the second risperidone use. In contrast to neuroleptics that are endowed with important adverse effects,<sup>48-50</sup> bumetanide is quite devoid of strong adverse effects, except hypokalemia.<sup>51</sup> The progressive changes observed in adults with schizophrenia<sup>50,52-54</sup> and the major roles that brain development plays in the pathogenesis of schizophrenia and autism<sup>55</sup> stress the need for early interventions that can be more readily performed with bumetanide than with spiridone and other antipsychotic agents. In conclusion, our observations call for wide range clinical trials and experimental investigations on the actions of bumetanide in schizophrenia.

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