

Diuretic Continues to Show Promise in Autism

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Megan Brooks, March 22, 2017

Treatment with the diuretic bumetanide (*Bumex*, Validus) improved core symptoms of autism spectrum disorder (ASD), including social deficits and stereotyped behaviors, results from a multicenter phase 2b study show.

Bumetanide was effective in improving ASD-related symptoms across the pediatric age range, as assessed by the Childhood Autism Rating Scale (CARS), the Clinical Global Impression Improvement scale (CGI-I), and the Social Responsive Scale (SRS), the researchers write.

"The drug worked in the sense that three of the classical scales for autism showed a significant improvement vs placebo," co-lead investigator Yehezkel Ben-Ari, PhD, president of Neurochlore, based in Marseille, France, noted in an interview with *Medscape Medical News*.

The study was [published online](#) March 14 in *Translational Psychiatry*.

"Striking" Results

In an [earlier phase 2 trial](#) involving 60 children with autism or Asperger syndrome, Dr Ben-Ari and colleagues found that a 3-month course of daily bumetanide reduced the severity of autism symptoms in three quarters of the children. As expected, hypokalemia, a common side effect of bumetanide, was observed and treated with potassium supplements.

The phase 2b study was conducted primarily to assess dose/response and safety effects of bumetanide. Participants included 88 ASD patients aged 2 to 18 years (78 boys, 10 girls). They were randomly allocated to receive bumetanide 0.5, 1.0, or 2.0 mg twice daily or placebo for 3 months.

Thirteen patients in the bumetanide group discontinued before the end of the study because of adverse events or other reasons. Of those patients, four had moderate hypokalemia, five had adverse events related to diuresis, two had difficulties complying with the study protocol, one was lost to follow-up, and there was one error in diagnosis.

In the placebo group, one patient discontinued because of difficulties complying with the study protocol, and one because of the use of concomitant psychotropic medications. Therefore, 73 of the 88 patients completed the trial (20, 19, and 13 patients, respectively, in the 0.5-, 1.0-, 2.0-mg bumetanide groups and 21 in the placebo group).

The mean initial CARS scores were similar across all treatment groups and were above the cutoff for severe autism, as required by the European Medicine Agency (>34), the researchers note.

For those patients who completed the trial, the mean CARS values decreased from baseline to 3 months, and the difference between all treatment groups was significant (Kruskal-Wallis $P = .015$). The greatest average change was in the bumetanide 2.0-mg group (-5.35), and the smallest was in the placebo group (-1.79; pairwise comparisons $P = .017$).

Twenty-three bumetanide-treated patients showed more than a 6-point reduction in CARS score from baseline to 3 months compared with only one of the placebo-treated patients, the researchers report.

Treatment with bumetanide significantly improved CGI-I score at 90 days ($P = .004$) and the SRS score by more than 10 points ($P = .020$), the investigators say.

"The results with CARS are striking when assessing the trial's completers (73 out of 88)," they write. "Significant effects were also observed with other scales including CGI and the parent-rated SRS total score with an improvement of more than 10 points considered clinically relevant."

In line with their earlier single-center trial, social communication and restricted interest were the most consistently improved behaviors noted by the parents in the SRS subscales.

"Interestingly, responders were found in all subpopulations, ages and ASD severity according to CARS scores suggesting that the treatment is not restricted to a particular group," the researchers note.

Approved in Europe

The most frequent adverse events were hypokalemia, increased urine elimination, loss of appetite, dehydration, and asthenia. Hypokalemia occurred mainly at the beginning of treatment with twice-daily doses of 1.0 and 2.0 mg. It improved gradually with oral potassium supplements. The frequency and incidence of adverse events were directly correlated with the dose of bumetanide.

The drug showed a favorable benefit/risk ratio at a dose of 1.0 twice daily. This finding will be tested in an upcoming phase 3 study, the researchers note.

Key limitations of the phase 2b study include the small sample size and the short observation period. In addition, the lack of information on predictors of treatment response, such as IQ, schooling, and comorbidity, "hampers the conclusions because of the extreme heterogeneity of ASD, and our future clinical trials will have to incorporate these measures. Finally, the diuretic actions of bumetanide also impact the blinding procedure," the researchers note.

"Another Exciting Chapter"

"This is another exciting chapter in a series of pilot studies on bumetanide in ASD," Jeremy Veenstra-VanderWeele, MD, associate professor of psychiatry at Columbia University

Medical Center in New York City, who was not involved in the study, told *Medscape Medical News*.

"The underlying hypothesis is fascinating, that manipulating chloride levels may allow enhancement of the inhibitory actions of GABA in the brain. The potential benefit seen in this dose-finding study is promising and bears following up in a larger study," said Dr Veenstra-VanderWeele.

Dr Veenstra-VanderWeele noted that it is "particularly challenging to blind families to treatment assignment when the medication being studied is a diuretic.

"The investigators were careful to separate assessment of adverse events from benefits, which is critical in a study such as this. Challenges remain, however, when the majority of participants at the more effective doses were instructed to enrich diet for potassium or were provided with a potassium supplement, whereas this never occurred on placebo."

Dr Ben-Ari and colleagues point out that the current study should be viewed as a "source of data" on the safety and dose-ranging usage of bumetanide, "and it provides further support to justify a large multisite European phase 3 trial."

Dr Ben-Ari told *Medscape Medical News* that the phase 3 study, which is approved by the European authorities, will be performed in about 400 children in five EU countries. The patients will receive 1 year of treatment, and they will reflect the entire pediatric autism population.

"We hope to get the drug on the market in Europe for autism by the end of 2021," he said.

Sunil Mehta, MD, PhD, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, told *Medscape Medical News* that the study is "noteworthy because it provides preliminary data suggesting efficacy in reducing symptoms of ASD from a drug class that previously hasn't been tried in ASD.

"We should interpret its results cautiously because it was designed mainly to decide what dose was safe to use in a larger efficacy trial, so we can't be sure how well this drug works in terms of reducing symptoms," said Dr Mehta, who was not involved in the study.

"It also appears that for their primary outcome measure (CARS score), both placebo and drug groups showed improvement to a similar level by the end of the study, but the relative change appeared larger in the drug group because they were more severely affected to start with," added Dr Mehta.

Funding for the trial was provided by an investment of Symmetry Capital, a grant from France's Agence Nationale de la Recherche, and French government loans. The study was sponsored by Neurochlore, a biotech company developing novel therapies for autism and other developmental disorders. Dr Ben-Ari and two coauthors are founders and shareholders of the company. The remaining authors have disclosed no relevant financial relationships.

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