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Treating Autism with Bumetanide: Are large multicentric and monocentric trials on selected populations complementary?

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Bruining and colleagues conclude that Bumetanide does not attenuate ASD despite a nominally significant treatment effect in repetitive behaviors (RBS) which is a core-symptom of ASD but was defined as a secondary measure in this trial¹. Four earlier studies performed by three independent institutes, including two that are not referred to by Bruining and colleagues^{2,3}, tested a total of 169 children -vs 122 placebo- have shown a significant amelioration of ASD symptomatology. Bumetanide also significantly attenuated behavioral features of patients with Tuberous Sclerosis according to Bruining and colleagues⁴. It is interesting to discuss the reasons underlying these discrepancies.

If Bruining highlights fair limitations to this trial, it appears to us that these haven't been discussed in relation to the placebo response observed. Bumetanide seems to have suffered from an important placebo response that made the drug unable to reveal its efficacy on the primary criterion. Three major aspects may have contributed to this high placebo response: a different population than the one studied in previous Bumetanide trials, complex and heavy assessments and the single site context.

i) Population selected:

It has often been shown in clinical trials in psychiatry the necessity to have a well characterized population in terms of clinical diagnosis and that the more severe the population is, the higher will be the sensitivity to reveal the efficacy of a drug. The population selected in this study had a threshold close to or below the generally admitted ADOS cut-off criteria (7 for ASD and 9 for autism for Module 3, and 7 for ASD and 10 for autism for Module 4): a threshold score of 6 and a mean score of 8.96 for the placebo group and 9.36 for the Bumetanide treated group is inferior or equal to the usual score for autism. Patients had also fluent language, an IQ >55 and SRS-2 values well below the one considered significant for difficult social problems (80 versus 100 in earlier studies). Therefore, many children included may not have met the criteria for an autism diagnosis or if they met the criteria, they were not severely affected.

ii) Multiple assessments

It has also been demonstrated that if the complex or heavy assessments or their multiplication may lead to difficulties revealing the efficacy of a drug, as both arms are suffering from a substantial burden. The concomitant tools used in parallel (EEG, cognitive tests etc.) for exploratory purposes were not used in earlier studies and may have also contributed to the low sensitivity of the trial to reveal drug efficacy, the primary assessment.

iii) Monocentric study

Bruining does not discuss the limitation that this study was conducted in a single site. If unfortunately, the site has generated unconsciously a high placebo response, this cannot be balanced by other sites as it would be in a multi-center trial.

There are some other differences to highlight.

- Bruining and colleagues discuss their trials results based on the outcome measure chosen. SRS-2 (parent/caregiver rated scale) used in this and earlier studies, remains a validated tool that is proposed to be used for development in ASD in the EMA guideline. However, Bruining et al criticize the clinician rating scale (CARS) as being inadequate without explanation; yet, this was used as primary endpoint in earlier studies and is proposed in EMA guideline. CARS raters were blinded from all other clinical and safety assessments.
- The dosage used here (1.0mg twice daily) has not shown the best benefit/risk ratio in previous trials. The 0.5mg (twice daily) has been retained for further development.

In conclusion, there are a number of differences between this and previous trials that underlie the different outcomes and conclusions. Selecting a specific population relying on biomarkers might facilitate the success of the trial and provide important information on the underlying pathogenic events. Yet, parents' requests are to develop treatment suitable for all children with autism, including the youngest and most severely inflicted. In this aim, large populations trials are instrumental, they will also provide a better understanding of the links between treatment and subgroups.

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