Clinical Outcome Assessments Used/Recommended by the EMA and FDA
for the Evaluation of Products to Treat Autism Spectrum Disorder

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Methodological Question Being Addressed

This poster intends to address the methodological question of which clinical outcome assessments (COAs) to select and include in the evaluation of products for the treatment of autism spectrum disorder.

Introduction (Aims)

Autism spectrum disorder (ASD) is a group of developmental disorders characterized by disturbance in language, perception and socialization. autistic children have problems with verbal and nonverbal communication, troubles with social interaction, and present repetitive behaviors or obsessive interests [1]. Under the DSM-5 criteria, individuals with ASD must show symptoms from early childhood, even if those symptoms are not recognized until later. This criteria change encourages earlier diagnosis of ASD but also follows people whose symptoms may not be fully recognized until social demands exceed their capacity to receive the diagnosis [2].

In the European Union, prevalence rates were estimated at a range between 30 and 63 per 10 000 (all forms of ASDs included) [3]. In the USA, the 2010 CDC estimates indicated that 14.7 per 1,000 8 year old were identified with ASD [4]. Prevalence is rising in both geographical areas.

There is no cure for ASD. However, behavior and communication approaches, dietary treatments, and medication can be used to relieve some symptoms and behaviors.

The objectives of this study were:
1. To review which guidance were published by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to help industry prepare marketing authorization applications for medicinal products for ASD treatment;
2. To identify which products were approved specifically for ASD; and
3. To find out about the use of clinical outcome assessments (COAs) in the approval process. COAs measure a patient’s symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithms, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer. There are four types of COA measures: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) measures.

Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD)

The review revealed major discrepancies between the FDA and the EMA, with no products approved in Europe, while two were approved in the USA (however non-specific to ASD); no guidelines available in the USA, and draft guideline developed in Europe.

COAs (ObsRO and ClinROs) played a major role in the evaluation of medicinal products approved for ASD in the USA. With globalization of research, more harmonization is needed between both agencies.

Disclosure: The authors report no conflicts of interest for this work

Results

The search of guidance revealed that only the EMA Committee for Medicinal Products for Human Use (CHMP) has adopted a draft guideline on February 25, 2016, on the clinical development of products for the treatment of ASD (Figure 1). In this guideline, the section devoted to ‘Methods to assess efficacy’, the CHMP recommends the following:

- Information should be obtained from at least one reliable informant and also from the subject (self-reported ‘subject’ rating scales) where this is possible. For children both the caretaker and teacher should provide data where possible. In adults and adolescents the specified reliable informant will depend on the symptom and functional severity of the individuals being studied.

- Symptomatic scales

  Symptoms should be assessed with scales validated for the full age range of patients to be studied. The use of the same rating scale for inclusion, efficacy and responder definition is recommended wherever possible. Scales based on clinician ratings using information obtained from reliable informants are most appropriate as primary efficacy measures. Both raters (clinicians) and observers (parents, caretakers, teachers etc.) should be adequately trained, including recording of data in observer diaries or into a database. Industry standard methods should be implemented to assess inter-rater reliability.

- Functional scales

  No validated scales of functioning have yet been clearly identified that would be specific to ASD. Functional scales developed for other conditions (e.g., ADHD) might have questionable applicability to ASD and might lack sensitivity for detecting a treatment effect in ASD patients. The development of a functional scale validated for autism is therefore encouraged. Adaptation of an existing functional scale, developed for another condition but adapted as appropriate for the specific requirements of a clinical trial in ASD, is a possible approach.

Global scales

The Clinical Global Impression - Improvement (CGI-I) scale is a well-established research rating tool applicable to psychiatric and neurological disorders that can be easily used by the practicing clinician (Guy et al., 1976; Bursztyn et al., 2007). However, it cannot be considered as a measure of function but as a global measure that reflects both core symptoms and functioning.

The FDA has approved only two products with an indication of autistic disorders, i.e., risperidone and aripiprazole; two atypical antipsychotics for control of behavioral symptomatology. No products with this indication could be found on the EMA website. The main criterion of evaluation for the FDA approved products was changes in symptom scores by COAs (Table 1).

- Risperidone and aripiprazole used the Aberrant Behavior Checklist (ABC), a measure completed by caregivers (ObsRO), to assess changes in irritability (primary endpoint). Secondary endpoints involved the use of ClinROs: the Clinical Global Impression - Change (CGI-C) scale (risperdone), and the CGI-I scale (aripiprazole) to measure changes in irritability.

Table 1: Products Approved by the FDA with the indication of treatment of irritability associated with autistic disorder

<table>
<thead>
<tr>
<th>INN</th>
<th>Brand Name</th>
<th>Marketing Authorised Holder</th>
<th>Date of Initial Approval</th>
<th>Labeling claim</th>
<th>CGI-I measure</th>
<th>Type of COA</th>
<th>End-point measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone</td>
<td>Risperdal</td>
<td>Novartis</td>
<td>12/01/2002</td>
<td>significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo.</td>
<td>CGI-I</td>
<td>CGI-I</td>
<td>irritability</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>Abilify</td>
<td>Otsuka</td>
<td>09/2002</td>
<td>[clinically significant improvement in]</td>
<td>CGI-C</td>
<td>CGI-C</td>
<td>irritability</td>
</tr>
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For more information, please contact: Catherine Acquadro, cacquadro@mapigroup.com, www.mapigroup.com

Methods

This research was conducted on the FDA and EMA websites (http://www.fda.gov/Drugs/default.htm and http://www.ema.europa.eu/ema) through a systematic manual review of ASD-specific EMA and FDA regulatory guidelines, product labeling and corresponding assessment reports or medical reviews.

Mapi’s PROLabels database (https://eprevide.mapi-trust.org/) was used for labeling claim identification. Off-label uses were not included.

Table 3: Products Approved by the FDA with the indication of treatment of irritability associated with autistic disorder

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I. References

II. Further reading