Evaluation of Drugs in Autism

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Abstract
Autism is a psychiatric illness with high burden for the patient family but without pharmacological treatment. The pathology of autism is not yet well defined but it seems to be a developmental illness as is schizophrenia but affecting other brains areas. It is proposed in the present paper for studying drugs in autism some inclusion and evaluation criteria mainly to treat symptomatology. It is as well proposed some therapeutic advises to treat some behavioural symptoms.

Keywords
Autism; Antipsychotics; Clinical Trial; Glutamine; Secretin

Introduction
Autism is a serious psychiatric illness that begins in early childhood. At present, there are no drugs which have proved effective in this pathology, in particular insofar as the pathology is poorly defined [1].

It seems, however, that it is a cerebral development disorder like schizophrenia but affecting other areas. It appears that there is an increase in the density of cells in the hippocampus and the amygdala with a decrease in dendritic connections and in the size of the cells. Moreover, there are also anomalies of the limbic system with cerebellar abnormalities without motor disorders.

Randomized, double-blind, placebo-controlled clinical studies remain the most appropriate method for evaluating the efficacy and safety of treatment [2]. While efforts are being made to elucidate the genetic and neurophysiological basis of autism, there is a need for psychiatrists and families to validate information to treat autistic patients. The aim of this article is to propose methodological tools for this evaluation.

Inclusion Criteria
There is no precise definition of autism, a constellation of behaviors are observed. The heterogeneity of the psychopathology and of the target symptoms makes the study of any treatment difficult. It is therefore necessary to focus on some characteristics of autism.

- Abnormal or altered development of social interactions and communication
- Stereotyped Activities
- Posture abnormalities
- Q.I. low (35-50) with cognitive impairments that are difficult to measure.

The heterogeneity of the symptoms therefore induces the heterogeneity of the pharmacological targets, since the two attitudes can be envisaged:

- improvement of one or more symptoms
- slowing down the evolution of the morbid process.

At present, the most commonly targeted therapeutic targets are:

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- aggressive behavior (valproic acid, carbamazepine, propranolol)
- attention deficit with hyperkinesia (clonidine, d-amphetamine)
- improvement of Q.I. secretin in patients with gastrointestinal disorders [3].

All of the drugs used have never been validated by rigorous clinical trials, they are more palliative drugs.

In order to define the inclusion criteria, it is therefore advisable to try to link one or more symptoms to a pharmacological target: serotonin, dopamine, glutamate or the like.

Two biological facts are in fact established, most of the time patients have high blood serotonin concentrations suggesting that they have a disorder of tryptophan metabolism. Another hypothesis would be the presence of a glutamatergic disorder.

It therefore seems logical to make an inventory of the symptoms and then include the patients whose predominant symptom is easily detectable or evaluable. The problem is that the most frequent symptoms are not specific to the disease (aggressiveness, stereotypes, for example). The quality of diagnosis depends largely on standardization.

The most suitable tool seems to be: Autism Diagnostic Interview-revised (ADI-R, 1994) it is a questionnaire of 111 items to be filled (2 to 3 hours). There is also a short version.

The ideal would certainly be the extent in which autism has been observed to increase the volumes of the total brain, the temporal parietal lobe and the cerebral hemispheres, but also the abnormalities of the amygdala, the hippocampus and the corpus callosum [4].

Evaluation Criteria

The ADI-R acts both as a diagnostic tool and as an evaluation tool. The items are scored from 0 to 3. Furthermore, the ADI-R is divided into subscales to evaluate the alterations in social relations, communication and behavior. This tool, on the other hand, is not very useful for evaluating other disorders such as the Pervasive Developmental Disorder (PDD) and Asperger’s syndrome. To assess the severity of the disorder, the CGI is not sensitive enough.

CY-BOCS, which is commonly used in OCD, can be used to evaluate the respective conduits. This scale can be used provided that the intercrossing deviations are close to 15%.

Other assessment tools can be used when the Aberrant Irritability Scale (ABC) is a behavioral scale completed by the parents or accompanying person. It is a question of characterizing the target symptoms and especially the 2 symptoms that concern the environment most. In autistic cognitive measures are difficult to perform due to low Q.I and aggressiveness and hyperactivity.

Direct observation (RITVO-FREEMAN REAL LIFE RATING SCALE) [5]. Measures the most important and most common symptoms; it allows following an evolution especially when using antipsychotic medications.

It would be important to define the responding patients by continuing the CGI with a 25% decrease in the irritability scale (ABC).

Proposal to Study a Drug in Autism

In the absence of specificity of action, it would be appropriate to evaluate the different antipsychotics in autism: clozapine, risperidone, olanzapine, etc. Focusing on a target symptom, hoping that the more or less specific activity of these substances on a receptor subtype. Taking the example of the aggressiveness encountered in animals (5-HT1B mice), it is possible to think that 5-HT1B agonists may decrease the aggressiveness of autism. Therefore, target symptoms and one or more receptor subtypes should be matched to provide a better understanding of the efficacy of drugs in autism.

There are no known efficacious treatments for the core social symptoms, although effects on repetitive behaviors are indicated with some data. While studies of fenfluramine, secretin, opiates, and mood stabilizers generally find no effect, mixed results suggest more research is needed on antidepressants and atypical antipsychotics. Newer lines of research, including cholinergic and glutamatergic agents and oxytocin, will be of considerable interest in the future. However, research on the treatment of core symptoms is plagued by limitations in study design, statistical power, and other issues inherent to the study of treatments for autism (e.g., heterogeneity of the disorder) that continue to prevent the elucidation of efficacious treatments.

In all studies, the reference product should be placebo to the extent that no treatment has demonstrated its validity [6]. A more complicated problem is that of the cerebral developmental disorder that should be treated very early [7].

References


