
# Psychosis and ASD

# 4

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## 4.1 Clinical Evaluation

The strict relationship between psychosis and ASD was present since the first definition of "autism" itself.

Kanner, in his description of the first autistic patients, took the term "autism" from Bleuler, who had collocated this characteristic within the core clinical symptom of schizophrenia [1, 2].

Initially and until the *DSM III*, we observed an almost complete overlapping between "childhood schizophrenia" and ASD. This overlapping was followed, later, by a rigid division of these two disorders, without the possibility of comorbidity; now, in the *DSM 5* [3], it is possible to define comorbidity between autism and schizophrenia when both the positive symptoms of schizophrenia (SCZ) and the characteristics of ASD are present in a patient [4].

A considerable number of ASD patients meet the criteria for a psychotic disorder (12–15%) [5–7].

Up to 40% of ASD patients meet formal criteria for a schizotypal personality disorder.

Autistic behavior traits may overlap with the schizotypal and schizoid ones [8].

We described through case series the possible clinical characteristics found in the comorbidity between psychotic disorders and ASD [9].

We observe several different types of relationship between psychosis and ASD.

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### 4.1.1 Misdiagnosis of Psychosis Instead of ASD

It is possible in clinical practice to observe patients diagnosed with schizophrenia or schizotypal personality disorder that are non-recognized ASD. This possibility is more frequent in older patients in Europe and in higher functioning autism, especially Asperger syndrome, because this syndrome was unknown in the past to psychiatrist who considered only Kanner's autism. So, a misdiagnosis of schizophrenia instead of ASD could be related to the historical data that nosographic description of Asperger syndrome, defined in 1944 by Hans Asperger, was not yet diffused in Europe since its translation made by Lorna Wing. Thus, persons with Asperger syndrome (now defined as ASD level 1 in *DSM 5*) who received a diagnosis from psychiatrists before this period were frequently considered part of other diagnostic categories instead of ASD and, in primis, schizophrenia.

We observed several cases of ASD misdiagnosis that share common clinical features [10]. All are characterized by normal verbal communication and fluent grammar, and all were brought to the attention of a physician because of relational problems, perceived not by the patient but by his/her family members or school teachers. Behaviors concerning interpersonal communication difficulties and patterns of repetitive behavior are less commonly perceived by the patient and his/her environment as a good reason to visit a doctor. The correct diagnosis could be made only after considering all the clinical features and especially a detailed developmental history of their early childhood that is the clinical key for distinguishing SCZ from ASD. Otherwise, if only a single cluster of symptoms is taken into account without neurodevelopmental patient data, cases can easily suggest other psychiatric or personality disorders, which are more familiar to the psychiatrist. Thus, aberration in language and apparently bizarre behavior can induce a misdiagnosis of schizophrenia, and chronic social withdrawal and difficulty in relationship with others can induce a misdiagnosis of schizoid/schizotypal personality disorder and so on.

The negative and catatonic manifestations of SCZD are similar to the social withdrawal and communicative difficulty in ASD that even specific tests, such as the Autism Diagnostic Observation Schedule (ADOS) [11], sometimes fail and produce false ASD positives if performed on adolescent patients with SCZD [12].

Also the RAADS—*Ritvo Autism and Asperger's Diagnostic Scale-Revised* [13]—evaluation must be related to patient neurodevelopmental history and not used as unique test to differential diagnosis between ASD and SCZ. The same is for Minnesota Multiphasic Personality Inventory (MMPI), if used as self-reported test, because persons with autism (PWA) may answer to question literally, and this may lead to misdiagnosis of psychosis. Rorschach test could be useful in ASD to detect psychotic functioning [14]. ADI-r interview could help clinician to a correct analysis of first years of patient's life, but in Asperger syndrome we can also observe false negative in ADI-r because symptoms are detected only when the child go to school, where higher social skills are requested [15].

One of the distinguishing features of schizoid personality disorder is a marked narrowing of effect with an impaired capacity for emotional experience and

expression. Differently from ASD, schizoid personality disorder does not show pleasure in sexual and affective relationship and does not really want others; on the contrary, PWA generally lack the social skill to easily get a sexual or affective relationship or to have a family, but they like it.

Schizotypal personality disorder is typified by seemingly eccentric social contact behavior with apparently paranoid perceptual distortion and bizarre convictions (magical thinking), but differently from schizophrenia, there aren't delusions or hallucinations.

Persons with ASD are hypomentalizers and fail to recognize social cues such as verbal hints, body language, and gesticulations, but persons with schizophrenia-like personality disorders tend to be hypermentalizers, overinterpreting such cues in a generally suspicious way. Most people with schizophrenia and schizophrenia-like personality disorders displayed well-adapted social behavior in childhood, along with apparently normal emotional function. Autistic signs are common in adolescents with schizotypal personality disorder, but autistic features are not linked with conversion to psychosis [16].

### 4.1.2 Autistic Pseudopsychosis

Persons with autism (PWA) may consider the reality from a literal point of view. So they can misread a joke as a serious event. They may also react to a change of their rigid routine or to a hypersensoriality stimulus (visual, noise, etc.) with tantrum or irritability, or psychomotor agitation apparently without significance. So they may be driven to Emergency Psychiatric Ward and diagnosed as acute psychosis.

A challenge behavior may also be related to physical pain that the persons with autism (PWA) are unable to describe.

Also a typical autistic meltdown, with psychomotor agitation, or an acute shutdown, with acute social withdrawal, linked for example to a sensory or activity overload, could be misdiagnosed as an acute psychotic episode.

So, visiting a PWA with psychomotor agitation, we have to first check some of the following items:

1. Is there pain? Is there an organic cause of the agitation? Is it possible to use a drug for pain such as paracetamol to detect this possibility? The PWA must be examined from an organic point of view.
2. Has the PWA routine changed and was he not prepared to change? We have to collect information from parents, social workers, etc.
3. Is there a sensorial stimulus as a trigger of agitation? We must know the characteristic of PWA, and his reaction to specific sensorial stimulus.
4. Does the PWA have difficulty to understand the environment? We must know that PWA may have difficulty in prosody or may detect external situations from a single detail and that if we change a single detail, it is a "world change" for the PWA, and that he prefers visual communication, so we have to explain how to read the reality correctly.

### 4.1.3 Transitory Reactive Paranoid Psychosis

In patients affected by ASD, and in particular in the Asperger syndrome, the scholastic or work discrimination is a frequent event and represents a stressful trigger that in turn elicits anxiety, depressive, and transient psychotic episodes. This happens in particular when a patient does not know to be affected by ASD (especially by Asperger), and thus, he does not know how to adequately relate or comprehend the hostility of the external environment, considering that often this hostility is caused accidentally by the patient behavior itself: he does not understand the world and the world does not understand him.

Clinicians must be careful because an acute paranoid psychosis could cover a misdiagnosed ASD.

### 4.1.4 Comorbidity of ASD and Paranoid Personality Disorder and/or Narcissistic Personality Disorder

Personality disorders may be observed in comorbidity with ASD. In these patients, we observe two distinct aspects: The classical "vengeance" thirst proper of a paranoid personality, associated with a narcissistic aspect (e.g., reflected in their need to write to the maxim authority) and also the ingenuity of the Asperger syndrome, (the patient could describe to unknown people his private life in public Facebook profile).

The presence of these comorbidities renders complex the treatment of Asperger syndrome because the narcissistic paranoid aspects are amplified when they are under the stress of a relationship and when they have to work with other people, and difficulties in relationship are also strictly related to Asperger syndrome, so it became a circuit that could lead to acute psychotic paranoid episodes.

### 4.1.5 Schizophrenic Evolution of an ASD

Some patients, diagnosed with ASD in their childhood, show a schizophrenic development in adolescence or adulthood, accompanied by neurodegenerative aspects and cognitive impairment [9].

As we know, we cannot wait for positive symptoms of psychosis (as requested in *DSM 5*) to diagnose this "comorbidity" (or, better, this psychotic evolution).

We must take care to a decline in cognitive functioning and in academical results that could be a symptom of the ASD neurodegenerative evolution toward schizophrenia [17–24]. School performance is a point of strength in high functioning ASD and especially in Asperger syndrome, so a decline is not usual in ASD without comorbidity. Visuospatial processing impairment and some memory deficits are apparent before the full expression of psychotic illness, and ultra-high risk patients who develop psychosis have impairment in the visual reproduction subtest and verbal memory index owing to low logical memory scores of the Wechsler Memory Scale [23]. In schizophrenia, negative symptoms are related to a pervasive pattern of worsening performance across a

broad range of neuropsychological function as verbal memory, abstraction and executive function, perceptual and motor speed, attentional function, and vigilance. Sustained attention and working memory deficit are trait markers of schizophrenia not consequent to delusions or side effects of drugs. Also a selective impairment in the attentional ability to inhibit prepotent response during attentional task (as detected by Stroop index color-word) is related to psychosis. Crystallized verbal skill is related to impairment in neurocognitive function and performance-based skills in everyday life function [25]. A neuropsychological evaluation of ASD patients may help to detect cognitive worsening, that if related to patient functioning impairment could be a marker of psychosis; in this situation, we can help patients before that full-blown positive symptoms (delusion and hallucinations) occur, as requested in *DSM 5*. Useful tests for clinical practice are Wechsler Intelligence Scale, Repeatable Battery for the Assessment of Neuropsychological Status—RBANS, the MATRICS Evaluation, the Brief Assessment of Cognition in Schizophrenia, the Brief Cognitive Assessment, and the Social Cognition Assessment [26, 27]. A neurocognitive rehabilitation treatment could be useful in this situation and also in detecting of trigger events to avoid them [28].

### 4.1.6 Affective Psychosis, Especially in Bipolar Disorder

In adolescence, an acute psychotic episode may represent the onset of a bipolar disorder, especially after the use of antidepressant drugs.

As described in the chapter of bipolar disorder, this comorbidity is higher in ASD compared to general population.

The first acute psychotic episode, also with delusion or hallucination, must not lead directly to a diagnosis of schizophrenia, because a psychotic mania is very similar in clinical presentation to schizophrenia, also with paranoid delusion that could also be present in mania.

## 4.2 Neurobiological Basis

There are numerous clinical and neurobiological links between SCZ and ASD that lead to hypothesize a deficit of a transdiagnostic cognitive circuitry linked to genetic–environmental pathogenesis of a unique neurodevelopmental disorder [17, 29–31].

Individuals with ASD and those with schizophrenia (SCZ) are characterized by marked social deficits, with impoverished social networks. Both groups are impaired in basic emotion perception. SCZ and ASD perform similarly to one another on social cognitive tasks and in social perceptual theory of mind [32].

ASD shows impaired performance on most domain of executive function (mental flexibility, sustained attention, and fluency), and early psychosis shows impairment on sustained attention and attentional shifting [29].

A substantial proportion of adults with schizophrenia (and bipolar disorder) show high autistic-like traits and symptoms, suggesting a shared pathophysiology among ASD and SCZ.

In schizophrenia, the distributed nature of brain region abnormalities suggests that multiple brain circuits are impaired, a neural feature that may be better addressed with network level analyses [33].

SCZ is related to neuropathological brain changes which are believed to disrupt connectivity between brain processes. In the first psychotic episode, SCZ patients show evidence of GM loss in cortical areas and in limbic structure as hippocampus, thalamus, striatum, and cerebellum. Consistent with disturbed neural connectivity, WM alterations have been observed in limbic structures, corpus callosum, and many subgyral and sublobar regions in the parietal, temporal, and frontal lobes [34]. Poor performance on the WCST in early psychosis subjects identifies those who have more marked cognitive impairment [35].

Even if schizophrenia spectrum disorder (SCZD), autism spectrum disorder (ASD), and obsessive compulsive spectrum disorder (OCSD) are considered in *DSM 5* as clinically separate psychiatric conditions with, supposedly, different brain alteration patterns, we described a meta-analytic study from a neuroimaging perspective aimed to address whether this nosographical differentiation is actually supported by different brain patterns of gray matter (GM) or white matter (WM) morphological alterations. Our analysis reveals that these psychiatric spectra do not present clear distinctive patterns of alterations; rather, they all tend to be distributed in two alteration clusters:

- Cluster 1, which is more specific for SCZD, includes the anterior insular, anterior cingulate cortex, ventromedial prefrontal cortex, and frontopolar areas, which are parts of the cognitive control system.
- Cluster 2, which is more specific for OCSD, presents occipital, temporal, and parietal alteration patterns with the involvement of sensorimotor, premotor, visual, and lingual areas, thus forming a network that is more associated with the auditory-visual, auditory, and premotor visual somatic functions. In turn, ASD appears to be uniformly distributed in the two clusters [36].

Studying the patterns of co-alteration distribution from voxel-based morphological data, we analyzed the patterns of brain alterations of SCZD, ASD, and OCSD. The analysis of the co-atrophy network of schizophrenia spectrum disorder (SCZD), ASD, and obsessive compulsive spectrum disorder (OCSD) reveals that alterations in certain GM sites appear to be statistically related to alterations of other GM regions. Although this finding has already been proven to be the case in neurodegenerative diseases, it has never been found before in psychiatric conditions [37].

The clusters of co-altered areas form a net of alterations that can be defined as morphometric co-alteration network (MCN) or co-atrophy network (in the case of gray matter decreases). Within this network, specific cerebral areas can be identified as pathoconnectivity hubs, the alteration of which is supposed to enhance the development of neuronal abnormalities. Within the morphometric co-atrophy network of SCZD, ASD, and OCSD, a subnetwork composed of 11 highly connected nodes can be distinguished. This subnetwork encompasses the anterior insula, inferior frontal areas, left superior temporal areas, left parahippocampal regions, left thalamus, and right precentral gyri. The co-altered areas also exhibit a normal structural covariance

pattern which overlaps, for some of these areas (like the insula), the co-alteration pattern. These findings reveal that, similarly to neurodegenerative diseases, psychiatric disorders are characterized by anatomical alterations that distribute according to connectivity constraints so as to form identifiable morphometric co-atrophy patterns.

In particular, our results indicate that a small number of brain areas show a high degree of pathoconnectivity and only a few cerebral areas appear to be particularly co-altered with several other regions; so, regions that play an important role in the formation and development of the MCN can be thought of as pathoconnectivity hubs. Brain sites with the highest network degree were found to be the insula and the prefrontal cortices, which are also strictly connected with each other. These regions are therefore pathoconnectivity hubs and can be considered as primary altered areas, whereas the other brain regions, which have a lower network degree and appear to be connected only with specific pathoconnectivity hubs, can be considered as secondary altered areas. We identify within the MCN a "core" subnetwork composed of 11 nodes located in the insula, inferior frontal gyrus, superior temporal gyrus, thalamus, and right precentral gyrus. Some of these regions are involved in supporting the salience network, an essential part of the frontoparietal control system. The disruption of the functional integrity of this network would account for the executive deficits that are frequently observed across schizophrenia and ASD. Alteration of the areas forming the MCN may lead to a disruption of social cognition, which is frequently associated with ASD and SCZD [38]. Social cognition refers to our abilities to recognize, manipulate, and behave with respect to socially relevant information, including the ability to construct representation flexibly to guide social behavior. Amygdala is part of the structures that form the basis of social cognition, and bilateral damage to the human amygdala has been found to impair social judgments of trustworthiness and approachability of people based on their faces. There is a clear relationship between the aspects of functional outcome and social cognition in schizophrenia and autism.

The insula has a role in the integration of external sensory stimuli with emotions, the conscious perception of error, the generation and maintenance of a state of awareness associated with the body's condition [39–43]. The anterior insula is involved in interoceptive, affective, and empathic processes and is a part of the salience network integrating external sensory stimuli with internal states as a hub mediating interactions between large-scale networks involved in externally and internally oriented cognitive processing: dysfunctional anterior insula connectivity plays an important role in autism [44].

Our analysis reveals that particularly the anterior part of the insular cortex seems to be mostly involved in the formation of the MCN associated with SCZD and ASD.

The STG multimodal areas are involved in cortical integration of both sensory and limbic information implicated in the social perceptual skills. STG is thought to process the biological motion [45, 46] and has been associated with some verbal and nonverbal communication impairments observed in patients with ASD [47].

Precentral and inferior frontal gyri are involved in the mirror neuron system; GM thinning in regions associated with the mirror neuron system has been correlated with social and communication deficits in patients with ASD [48–51].

The disruption of the thalamus has been variously associated with SCZD and ASD, and a reduced GM density in the thalamus, right cerebellum hemisphere, and left temporoparietal cortex is related to intellectual disabilities in ASD [52]. Other findings suggest a relationship between hypoconnectivity disturbances in the thalamofrontal system and ASD [53]. The thalamus is also supposed to play an important role in the inflammatory processes.

In both ASD and SCZD, disruption of the loop system of the basal ganglia is thought to explain impaired sensorimotor access, which reflects the ability of an organism to filter out irrelevant stimuli; hippocampal disruption has been associated with both ASD and SCZD [54]. Hippocampal deficits are an established feature of schizophrenia and are complementary with evidences of marked allocentric processing deficits of psychosis; hippocampal could be viewed as a cognitive map, with spatial maps built in right hippocampus and semantic maps in left hippocampus.

The fact that neuronal abnormalities caused by SCZD and ASD converge on a set of core areas that are associated with cognitive control functions [55, 56] is also consistent with previous evidence showing that in brain disorders GM alterations and WM alterations tend to exhibit concordant patterns of distribution, which are influenced by brain connectivity [57–60].

Proteins such as astrotactin have been suggested as a common genetic link among these different spectra, because they are fundamental in guiding neuron migration during brain development [61].

Oxytocin, a hormone related to the regulation of social behavior and the formation of pair bonds, has been found to be involved in psychiatric disorders, including ASD and SCZD. In patients with ASD, oxytocin appears to be related to social recognition, attachment, and stereotyped behaviors, whereas in patients with SCZD it has been associated with a potential antipsychotic effect [62–66].

The relative symptomatic similarity between ASD and SCZD is consistent with a neurobiological model that suggests a common basis for SCZD and ASD, with a number of genetic alterations (SHANK 3 variations, DISC 1, dysregulation of CYFIP1, SCN2A, NRXN1 neurexin gene, or RELN), cytoarchitectural abnormalities (about proliferation, migration, and lamination defects), neuropsychological deficit, neuroimaging investigations (about GM/WM abnormalities and structural/functional connectivity alterations), and clinical observations [31, 67–74].

It is possible that there are genes that can be linked to the social cognitive defects, such as Disrupted in Schizophrenia 1 (DISC 1) gene, choroidal neurovascularization disruption of the neurexin-1 (NRXN1) gene, in both SCZ and ASD.

Autistic-like traits, detected also with Social Responsiveness Scale for Adults, are higher in subjects with schizophrenia and bipolar disorder than in general population, suggesting a shared pathophysiology among ASD and SCZ and bipolar disorder [75]. The high "comorbidity" between ASD, ADHD, intellectual disability, SCZ, and bipolar disorder challenge the etiological basis of current diagnostic categories and suggest that we should consider neurodevelopmental disorders as a unique group of related and overlapping syndromes that result in part as a combination of genetic and environmental effects on brain development [76]. All the clinical data might be accounted for by finding out the common genetic roots at the basis of

neurodevelopment disorders, which bring about phenotypic expressions with different timings and modalities, due to epigenetic factors affecting the production of proteins with regulatory function over the brain organization and development [77]. This hypothesis is consistent with the clinical examination of families of patients with ASD, in which phenotypic expressions bear psychiatric disorders different from ASD and SCZD [78]. The relationship between genes, epigenetic, and environmental factors could emerge from the specific patterns of structural alterations, and brain hubs are likely to be the areas in which this relationship appears to be stronger. Both schizophrenia and ASD are highly heritable, with 25–33% genetic contribution to schizophrenia and 49% to ASD.

A genetic model of the link between SCZ and ASD could be the 22q11.2 deletion syndrome (Di George syndrome), a neurogenetic disorder affecting 1 in 2000–4000 live births. This syndrome in 90% of cases arises from de novo mutation and is associated with high rates of psychosis (41%) and ASD (14–50%); also ADHD is frequent in this syndrome (37%) overrepresented in males, and anxiety disorders and mood disorders, too [79]. Up to 30% of adolescents and adults develop a schizophrenia-like psychosis [80]. ASD and SCZ represent two unrelated phenotypic manifestations consistent with a neuropsychiatry pleiotropy model. This genetic lesion provides a unique model for the discovery of specific genome risk and potentially protective factors for neuropsychiatric disease. The rate of psychosis and mood disorders increases dramatically in adolescence and young adulthood, and a cognitive deterioration in adolescence is a dynamic phenotype that may be a potent predictor of psychosis in the 22q11 deletion syndrome. In this syndrome, we could also observe an early onset Parkinson's disease that suggests a role of a dopaminergic system disruption in older patients [80, 81]. Other than velocardiofacial signs, in these patients seizures could be observed, which are typically related to hypocalcemia, an easily identifiable specific factor [82–84].

The neurobiological substrate of common alterations in ASD and SCZS may involve a neurochemical unbalance, especially an alteration in the ratios of GABA–glutamate on the one hand and oxytocin–vasopressin on the other, which could be the targets of specific pharmacological therapies for ASD [85, 86], as balovaptan. In syndromic ASD, metabotropic glutamate receptor 5 (mGLUr5) CNVs are more prevalent; the dysregulation of the mGLUr network is a possible permissive factor that increases propensity to develop an ASD [87]. Deficits of synchronous firing of neurons required for higher order cognitive functioning have been observed in SCZ and have been attributed to deficits of GABA signaling-related mRNAs and proteins; also GABAergic neurons in the subcortical white matter are affected in psychosis [88]. ASD and SCZ have an overlap linked to social disorganization, and the high expression of the SD phenotype may be associated with increased glutamate/GABA ratio in the right auditory regions, which may affect prosody processing [85].

Several studies have supported a role of neuroinflammation in the etiology of ASD, SCZD, and other brain disorders [89, 90]. In fact, an increased inflammatory response in the central nervous system is supposed to activate microglial cells, the activity of which leads to the release of pro-inflammatory cytokines,

including interleukin (IL)-1b, IL-6, and tumor necrosis factor-a. In turn, pro-inflammatory cytokines aggravate and propagate neuroinflammation, thus degenerating healthy neurons and impairing brain functions. The activated microglia may contribute to the generation of GM abnormalities and, consequently, to the pathogenesis of psychiatric disorders [91]. Microglia is supposed to regulate excitatory and inhibitory input to pyramidal neurons [92]. Differences in neuroinflammatory response in individual immune response and environmental factors may explain different age of clinical onset of ASD and SCZ. The development of ASD, differently from SCZD, appears to be more related to cerebellar dysfunction and subsequent thalamic hyperactivation in early childhood. In contrast, SCZD seems to be triggered by thalamic hyperactivation in late adolescence, whereas hippocampal aberration can possibly originate in childhood. The possible culprits could be found in the metal homeostasis disturbances, which can induce dysfunction of blood–cerebrospinal fluid barrier. Thalamic hyperactivation is thought to be produced by microglia-mediated neuroinflammation as well as by abnormalities of the intracerebral environment. Consequently, it is likely that thalamic hyperactivation leads to the dysregulation of the circuit formed by dorsolateral prefrontal cortex and lower brain regions related to social cognition [37, 89].

Evidence support the role of neuroinflammation in the link between ASD and SCZ that involve microglia (the inflammatory brain-resident myeloid cells) and biomarkers (cytokines, oxidative stress markers, and microRNA players) that influence cellular processes at brain and immune levels.

Approaches of functional connectivity reveal that specific parameters of connectivity networks present heritability and are associated with familial risk for psychopathology, suggesting a genetic role not only with regard to single psychiatric categories but with regard to the brain inter-regional synchronization, thus confirming liability to broad dimensions of symptomatically related disorders [55, 93]. Mental illness is generally characterized by polygenic inheritance, which constantly causes genetic liability. This defies the validity of rigid categorical models of psychiatric disorder and risk, as it implies also that brain disorders can be viewed as the extreme manifestations of distributed quantitative traits; so the presence of ASD and SCZ in a patient could be viewed as a unique neurodevelopmental disorder, with early onset in ASD and late onset in SCZ. So it is not correct to describe the association ASD–SCZ in a patient as a "comorbidity," but we have to think better as a "schizophrenic evolution of ASD" or a late onset of a unique neurodevelopmental disorder, linked to common genetic basis, too [94].

## 4.3 Treatment

Otherwise, we must remember that ASD and SCZ need specific and distinct treatment and that if we observe a schizophrenic evolution of an ASD, we have to consider both the treatment, for psychosis and for ASD. ASD is not a psychosis, indeed.

Using antipsychotic drugs in ASD could be related to:

– Treating symptoms not related to ASD core symptoms, as irritability, and in this case risperidone and aripiprazole are FDA-approved drugs [95, 96].
– Treating true psychotic symptoms in ASD. This is related to the same treatment of psychosis than in general population.

We have to take care that ASD population may have very individually specific response to the drugs; so, the response to the specific drug and side effects are less predictable than in general population, and so the dose of the drug must be strictly personalized with a "tailor" technique, with frequent controls of the patient especially in the first period of treatment itself.

A role in pathogenesis and in the treatment of biological condition linked to ASD and psychosis could be related to microbiome. The extinction of key "heirloom" taxa can deprive individuals of metabolic pathways that have been present in their ancestors for millennia. Some of these pathways support essential synthesis and toxin clearance processes. So clinicians must pay attention to a microbiome equilibrium that could be one of the pieces of the complexity of the treatment [97].

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