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Medication treatment in subjects with autistic spectrum disorders

Abstract Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous. Twin and family genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair strategy has found a promising linkage to a region on chromosome 7. In 10–15 % of the cases autism is due to associated medical conditions that affect normal brain functioning. Post-mortem studies on small case series report cellular abnormalities in the limbic system and cerebellum. Between 10 and 20 % of subjects with autism have macrocephalia, which is in accordance with MRI findings of an increased total brain tissue volume and enlargement most prominent in the occipital and parietal lobes. The most robust and well-replicated neurobiological abnormality in autism is an elevation of whole blood serotonin found in over 30 % of the patients. Pharmacological interventions with serotonin reuptake blockers or with atypical neuroleptics that block both dopamine (D_2) and serotonin ($5\text{-}HT_2$) receptors seem to offer clinical benefit and merit further study.

Key words Autism – drug treatment – atypical neuroleptic – SSRI

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Introduction

This review aims to present the current theories regarding the pathogenesis of autism, and to draw implications for pharmacotherapy. Autistic disorder (autism) is the prototype of a pervasive developmental disorder (PDD) and is characterized by 1) qualitative impairments in reciprocal social interactions, 2) qualitative impairments in verbal and non-verbal communication, 3) restricted repetitive and stereotyped patterns of behaviour, interests and activities, and 4) onset prior to age three years (2, 131). The prevalence of autism is estimated at 2–5 per 10,000, with numbers expanding to 10–20 per 10,000 if broader definitions are used (76). The manifestations of autism vary greatly, depending on developmental level and chronological age of the individual. The majority of subjects with autism will exhibit serious social and communicative handicaps throughout life, but some will improve enough to be able to live relatively independently as adults. About 75 % of individuals with autism have associated mental retardation.

The category of PDD (DSM-IV) includes, along with autism, a number of related conditions, such as Rett's disorder, Childhood disintegrative disorder, Asperger's disorder, and Pervasive Developmental Disorder – not otherwise specified (PDD-NOS). Both Rett's disorder and Childhood disintegrative disorder are rare conditions. Rett's disorder has been reported only in females and is characterized by an apparently normal development until age five months, followed by deceleration of head growth and by loss of purposeful hand skills, and social and communication skills. Childhood disintegrative disorder is marked by significant regression in multiple areas of functioning following a period of at least two years of apparently normal development. While this condition is occasionally attributed to a paediatric neurological disease (e.g. metachromatic leucodystrophy) most cases however remain e causa ignota. The essential features of Asperger's disorder are impairments in reciprocal social interactions and restricted stereotyped patterns of interest (like in autism), along with relatively intact language skills at age two and three years (in

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contrast to autism). Additional features may be motor clumsiness and motor delays, and the disorder is usually recognized at a somewhat later age than autism, i.e. during the school age period. PDD-NOS is a residual category for those subjects who present with severe developmental problems typical of PDD but who fail to meet the criteria of any of the specific PDDs mentioned above. Recent work regarding diagnostic algorithms for PDD-NOS has described the condition as a subthreshold category of autism with at least four out the 12 criteria for autism present, including one of the social interaction criteria (18, 19). Though both Asperger's Disorder and PDD-NOS appear to be more common than typical autism, precise prevalence estimates are lacking. Since research on the pathogenesis and treatment of PDD has been focused almost exclusively on autism, the remainder of this paper will be limited to a discussion of autism. Pathogenesis refers to both the constellation of aetiologic factors to which the disorder may be ascribed and the neurobiological processes and abnormalities which may underlie aetiological mechanisms.

Aetiology

There is substantial evidence from twin and family genetic studies that autism has strong genetic components. The recurrence risk for autism following the birth of an autistic child is 60 to 150 times the population base rate (119). Epidemiologically based same-sex twin studies have reported much higher concordance rates for autism among identical than among non-identical twins (6, 41, 120). For example, in one study pair-wise concordance rate for autism was 69 % for identical twins and 0 % for non-identical twins (6). Further, both family genetic (11) and twin studies (6) found that the autism phenotype extends well beyond the traditional diagnosis and involves more subtle social, cognitive and communicative handicaps that are similar to autism in quality, but differ markedly in degree. The difference in pair-wise concordance rate between identical and non-identical twins is even larger when the broader phenotype rather than a narrow definition of autism is applied, and this results in heritability estimates of about 90 % (6). The mode of genetic transmission is unclear and the marked fall-off in rate of autism which occurs between identical to non-identical twins or siblings suggests that a small number of interacting genes rather than one single gene is involved (97). A recent full genome search for susceptibility loci in autism using affected sib pairs has resulted in linkage to a region on chromosome 7q (65). Replication studies and further fine mapping of this region, including tests for linkage dysequilibrium and analysis of candidate genes, are underway.

In 10–15 % of the cases, autism is associated with known medical causes that affect normal brain functioning (115). The percentage of associated medical conditions is as much as 35% for atypical cases, which satisfy the criteria of PDD-NOS, and is further a function of the severity of comorbid mental retardation. In part, these medical conditions associated with autism are also (mono-)genetic disorders such as Fragile X, tuberous sclerosis, neurofibromatosis, phenylketonuria etc. Environmental causes, such as infections due to congenital rubella, cytomegalovirus or herpes virus, have been described occasionally, but are in current practice quite infrequent causes of autism and, if operative, are most likely give rise to atypical symptomatology. An interesting question, of course, is by which mechanisms do these associated medical conditions lead to autistic symptoms. Is autism a non-specific sequelae of mental retardation or is it the result of disruptions in brain circuits which are specifically involved in social and communicative behaviours? Work on tuberous sclerosis suggests that the latter explanation is most likely, and that the extent and localisation of brain lesions is the key variable. Autism is significantly more common in tuberous sclerosis when, in addition to mental retardation, epilepsy is present and lesions are found in the temporal lobes and the limbic areas of the brain (12).

Obstetric complications have for some time been considered as an important environmental cause. This view was based on the finding that in discordant identical twin pairs the autistic twin was most affected by obstetric hazards (41, 120). Later findings, however, have strongly modified this view identifying that obstetric hazards are consequences of genetically influenced abnormal prenatal development rather than independent aetiological factors (13). These interpretations stress that 1) the obstetric complications in the twin studies mostly were very minor, 2) the association between obstetric hazards and autism in singletons is quite weak, 3) post-mortem studies of autism have not detected lesions typical of perinatal brain damage and 4) studies of autistic singletons have found that the number of minor congenital anomalies is higher in probands than in siblings or normal controls, which suggests that the early in-utero development of autistic individuals may be suboptimal (8).

Recently, attention has been drawn to a report on a consecutive series of 12 children with a history of pervasive developmental disorder who were reported to exhibit loss of acquired skills and intestinal symptoms, such as diarrhoea, abdominal pain and food intolerance. Extensive clinical investigations revealed a chronic inflammatory bowel disease, associated autism (N = 9) or related conditions (N = 3) and an absence of focal neurological abnormalities (124). According to the parents, the onset of behavioural symptoms was associated with recent measles, mumps, rubella vaccination in eight children, with measles infection in one child and with otitis media in another child. It was suggested that a dysfunctional intestine played a part in the behavioural changes of these children, possibly due to increased permeability to gut-derived

peptides from food which in turn may exert central effects and interfere with neuroregulatory processes. Treatment of the intestinal pathology, by prevention of constipation and administration of aminosalicylates, led to behavioural improvements in several children. The idea that some cases of PDD may be linked to a form of inflammatory bowel disease merits further research and confirmation. Among other issues, it should be clarified: 1) what percentage of children with inflammatory bowel disease present neuropsychiatric symptoms, in order to control for selection bias; and 2) to which extent do these children exhibit typical rather than atypical autistic symptoms. Conversely, studies indicate that a significant proportion of subjects with PDD have gastrointestinal symptoms, such as abdominal distension, constipation and chronic diarrhoea, which may be due to altered intestinal permeability (34). A key question to be answered, of course, is whether children with PDD without intestinal complaints should be referred to paediatric gastroenterologists for further investigations. The second idea of this report, the suggestion of a relationship between bowel disease/autism and vaccinations or viral infections is much more problematic and unsubstantiated since the relation may well be merely coincidental and not causal (24). A recent epidemiological report indeed failed to provide support for a causal association between autism and the measles, mumps and rubella vaccine (121). The potential importance of a brain-gastrointestinal axis in autism has been further emphasized by case reports on dramatic improvements of social and language skills of children with autism following administration of secretin (58). We will discuss this issue extensively later in this paper.

Neurobiology

There is overwhelming evidence that abnormalities of brain structure and brain function underlie the autistic syndrome. However, it is also clear that 1) reported abnormalities are rather heterogeneous and based on studies of small samples, 2) most reported abnormalities have not been replicated, 3) findings specific to the core social and communicative deficits have as yet not been demarcated from non-specific findings, and 4) neurobiological abnormalities have not been examined in a genetic perspective, leaving it open whether, where and to what extent genetic influences on autism produce aberrant brain morphology or brain function. In this section the focus will be on recent findings from post-mortem and brain imaging studies and on neurochemical evaluations. Neuropsychological, neurophysiological and cognitive studies fall outside the scope of this paper and interested readers may consult other recent reviews (6, 51).

Post-mortem studies

To date, there have been only a few autopsy studies in autism. Reduced cell size and increased cell packing density have been observed bilaterally in the hippocampus, amygdala, entorhinal cortex, mammillary body, medial septal nucleus and anterior cingulate gyrus (9, 66). These structures are known to be connected to each other by interrelated circuits and comprise a major portion of the limbic system of the brain. In the cerebellum a marked reduction of the number of Purkinje cells was found, along with a preservation of olivary neurons. This suggests that these brain lesions be of prenatal origin. Since it is now recognised that the cerebellum is involved in a variety of cognitive and affective processes, abnormalities of the limbic system and cerebellum may be linked to the core social and communicative deficits in autism. Another report, however, while replicating the reduction in Purkinje cells, did not substantiate the elevated neuronal density in the hippocampus and found more widespread abnormalities in the cortex and brainstem (7).

Brain morphology

Recent evidence using different samples has shown that macrocephaly occurs in 10–20 % of autistic individuals (6, 11, 130). This is an important finding since the mean head circumference of mentally retarded individuals in general is two or more standard deviations below the mean of normal children and adults. The age at which macrocephaly develops in autistic children is not yet known. An explorative study found abnormal rates of head growth in early and middle childhood in some (37 %) children with autism, with only a few children being macrocephalic at birth (73). Important questions for further research are at what age does macrocephaly develop, and whether rates of head growth in autism are related to clinical course and/or distinguish subtypes of autism. It should further be clarified to which extent macrocephaly is familial and does also occur in family members who do not themselves have autism.

Qualitative MR scanning has revealed cortical malformations in some subjects with autism which might indicate possible neuronal migration defects (101). Further, consistent with head circumference findings, a number of MRI studies of subjects with autism have found an increased total brain tissue volume (excluding CSF), which was regional and not generalized, with the greatest enlargement in the posterior regions of the brain, i.e. the occipital and parietal lobes (38, 98, 99). An area of controversy over the past several years has been quantitative MR imaging of the size of the cerebellum and the brainstem. Earlier claims of neocerebellar hypoplasia (31, 32) have not been replicated. On the contrary, recently total cere-

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bellar volume was found to be greater in subjects with autism than in controls, with the increase being proportionate to the increase in total brain volume (103). Findings that the pons, midbrain and medulla are significantly smaller in autistic individuals (53–55) are not in accordance with reports from other groups (63, 102) and are probably due to concomittant mental retardation rather than to autism. The size of the body and posterior subregions, but not of the anterior subregions, of the corpus callosum was noted to be smaller in subjects with autism compared to controls (100). Though the posterior localization of the abnormal size of the corpus callosum is consistent with the reports of volume abnormalities cited above, the direction of the size differences is opposite of what might have been predicted. All in all, the presence of brain enlargement may provide important clues to underlying abnormalities in brain development and asks for further clarification of the timing of brain enlargement through longitudinal studies. Three possible mechanisms have been proposed to explain brain enlargement: 1) increased neurogenesis, 2) decreased neuronal death, and 3) increased production of non-neuronal brain tissue. The finding of head circumference at birth being within the normal range and accelerated brain growth in the early postnatal period would be most consistent with the mechanism of decreased programmed cell death, since neurogenesis occurs foremost in the prenatal period.

Brain function

A number of recent functional brain imaging studies in autism point at the frontal lobes as an area of the brain potentially involved in the pathophysiology of the disorder. A SPECT study of regional cerebral blood flow reported a frontal hypoperfusion in children with autism at the age of three to four years, which was found to be no longer present at re-examination three years later (132). A ^{31}P MR spectroscopy study in adolescents and adults with autism provided evidence of an abnormal pattern of phospholipid metabolism in the dorsolateral prefrontal cortex (88). The severity of metabolic abnormality was found to be significantly correlated with executive function and language deficits.

Neurochemistry

Current interest in the neurochemistry of autism is focused foremost on serotonin (5-HT) and peptidergic systems. Studies of the dopaminergic and noradrenergic systems in autism have failed to reveal consistent abnormalities. The potential relevance of the dopaminergic system for understanding the pathophysiology of autism comes from observations in animal studies in which the dopaminergic system was found to be involved in hyperactivity and stereotyped behaviours. Neurochemical research in autism has included the measurement of the major metabolite of dopamine, homovanillic acid (HVA), in body fluids. The HVA levels in cerebrospinal fluid (26, 47, 48, 90, 114) and in urine (43, 50, 74, 77, 86) of subjects with autism have been found to be equal as well as increased, when compared to those of control and contrast groups. The excretion of dopamine in urine has been reported to be lowered, whereas higher levels of dopamine were measured in whole blood of subjects with autism (77). A recent PET study suggested a low activity of the frontal dopamine system in autism (36).

An elevation of the concentration of 5-HT in whole blood of individuals with autism compared to normal controls is one of the most robust and well-replicated findings in the neurobiology of autism (3, 30, 87). The elevation is commonly observed in over 30 % of all subjects with autism and the magnitude of the difference in mean level is about 25 %. The importance of hyperserotoninemia in autism, however, had remained unclear for at least two reasons. First, the CSF levels of 5-hydroxy-indoleacetic acid (5-HIAA), the breakdown product of serotonin, were not found to differ between subjects of autism and controls (47, 48, 90, 114). Secondly, hyperserotoninemia has also been reported in non-autistic subjects with mental handicaps (94). A recent attempt to resolve these inconsistencies regarding hyperserotoninemia in autism pointed to the importance of pubertal and racial factors, when interpreting serotonin levels (78). Hyperserotoninemia appears to be a function of pubertal status (measured in prepubertal but not in postpubertal autistic subjects) and was not found to be present in mentally retarded or cognitively impaired control subjects without autism (78). Though the mechanisms underlying hyperserotoninemia have not been fully clarified, increased activity of the serotonin transporter of platelets and decreased binding to the 5-HT$_2$ receptor have been observed (27). Preliminary findings from candidate-genes studies indicate that the short variant of the promoter of the serotonin transporter gene in one report (29), the long variant in another report (68), but not a polymorphism of the 5-HT$_2$ receptor gene, have been significantly associated with autism (57). The clinical relevance of hyperserotoninemia for autism is further strengthened by reports of positive correlations of whole blood 5-HT with clinical severity (57) and negative correlations with verbal-expressive abilities in autistic probands and their first-degree relatives (33). Findings concerning the central activity of 5-HT metabolism are mixed. Measurements of 5-HT metabolites in cerebrospinal fluid of autistic subjects have failed to demonstrate consistent abnormalities (90) but neuroendocrine responses to pharmacological probes of the 5-HT system were found to be blunted (59, 79), suggesting a low central tonus of the 5-HT system. Using radioactive L-tryptophan as a tracer for serotonin synthesis with positron emission tomography,

unilateral alterations of serotonin synthesis in the dentato-thalamocortical pathway in autistic boys were observed (25). Further, acute dietary depletion of tryptophan, a precursor of 5-HT, was associated with an exacerbation of stereotyped behaviours rather than with changes of social unrelatedness in drug-free adults with autism (83). Any implication of 5-HT in the pathogenesis of autism would be of great interest, given the critical role of 5-HT during embryogenesis and maturation of the brain and the modulatory effects of 5-HT on a variety of important processes, such as sensory perception, motor function, learning and memory, and sleep, which are all often perturbed in autism.

Since opioids have been found to be involved in maternal-infant attachment in animal studies by influencing feelings of social comfort and blocking separation distress reactions, it has been hypothesised that excessive activity of opioids systems in the brain would prevent the formation of normal social bonding in humans and contribute to the genesis and maintenance of autistic symptoms (93). However, research on β-endorphin levels in cerebrospinal fluid and in plasma of subjects with autism has yielded inconsistent results (122, 128). The finding that the concentrations of both β-endorphin and ACTH were increased in the plasma of subjects with severe autism in the absence of changes of plasma levels of cortisol most likely indicates that there is a heightened response to acute stressors rather than a chronic alteration of the basal level of functioning of these systems (122). Another peptide, which has been implicated in maternal-infant bonding and affiliative behaviour, is oxytocin (42, 64). The potential relevance of oxytocin for the pathophysiology of autism is reflected in recent findings that plasma levels of oxytocin were significantly lower in subjects with autism compared to normal controls, and that the pattern of associations with clinical measures was different for the autistic and the normal sample (89). It should be appreciated, however, that attachment behaviour and social bonding per se are not abnormal in subjects with autism and that any neurobiological account of autism should explain why some social and communicative behaviours are impaired whereas others are relatively intact (16).

Medication treatment

Given that the neurochemical basis of autism is unknown, there is as yet no place for a pharmacotherapy based on defined pathogenesis of the core social and communicative deficits. The exception, perhaps, are interventions in the 5-HT neurotransmitter system, which may be based on evidence for abnormalities in 5-HT metabolism in a subgroup of individuals with autism. Other interventions of clinical utility have been developed more from a pragmatic perspective. This is not to play down the importance of medications for subjects with autism in the treatment of distressing or maladaptive target symptoms, such as hyperactivity, aggression, excitement, negativism, and ritualised, stereotyped or self-injurious behaviours. Further, clinicians should not hesitate to treat comorbid disorders, such as major depressive disorder or bipolar disorder "lege artis" with medication. Drug treatment, however, should never be considered as a single intervention, and should always be a part of a comprehensive multidisciplinary treatment approach. When starting with medication, it is important to select appropriate targets of treatment and to monitor efficacy and side effects on a regular basis.

A comprehensive approach to the treatment of individuals with autism usually includes a combination of structured and special educational techniques, individual behaviour modification, home training, family counselling, and placement in special schools or day-care centres. Detailed information about the principles, indications and effectiveness of behavioural and psychological treatment interventions may be found elsewhere (61, 62).

Medication affecting serotonergic neurotransmission

Early studies with *fenfluramine*, a halogenated amphetamine that promotes the release and inhibits the reuptake of serotonin and blocks dopamine receptors, reported dramatic improvements (44, 113). However, the results of a subsequent large-scale multicentre trial and a number of independent controlled trials were mixed and initial claims could not be supported. In combination with the potential neurotoxicity of fenfluramine (118) and reports of serious side effects (111), this is sufficient reason not to recommend fenfluramine for clinical use (17). Moreover, in many countries fenfluramine has now been withdrawn from the market because of these concerns over its safety.

Clomipramine is a tricyclic antidepressant and a potent non-selective serotonin-reuptake inhibitor. Treatment with clomipramine led to improvements of social relatedness, obsessive-compulsive symptoms and aggressive and impulsive behaviour in four out of five autistic patients aged 13–33 years in an open-label design (85). These findings have been extended in another open-label study with clomipramine in 35 adults with PDD (14). About 55 % of these patients showed a significant treatment response and improved in repetitive thoughts and rituals, aggression and social behaviour. In a controlled study of autistic children between six and 18 years of age the response to clomipramine was compared to that of desipramine, a tricyclic noradrenergic uptake inhibitor (49). Clomipramine was found to be superior to desipramine in improving social relatedness and anger/uncooperativeness, while both drugs were superior to placebo in decreasing symptoms of hyperactivity. Since treatment with clomipramine

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may result in troublesome and potentially serious side effects, such as a grand mal seizure because of the lowered seizure threshold, anticholinergic and cardiovascular side effects and behavioural toxicity (116), our recommendation is to use these medications judiciously in children with autism.

Fluvoxamine, a selective serotonin-reuptake inhibitor (SSRI), proved significantly more effective than placebo in a recent 12-week, double blind, placebo-controlled trial with 30 autistic adults (84). From the 15 patients who received fluvoxamine, eight were categorised as responders. Except for mild sedation and nausea, fluvoxamine was well tolerated. A similar study with fluvoxamine in subjects with autism younger than 18 years, however, could not establish a significant treatment response but documented a high rate of side effects and adverse behavioural activation (80). Since fluvoxamine given in similar dosages to youngsters with obsessive-compulsive disorder (OCD) was found to be devoid of distressing behavioural activation (112), children with PDD may be particularly sensitive to serotonin uptake blockers. This suggests that the serotonergic system be differentially involved in PDD compared to OCD.

Two other SSRIs, *fluoxetine* and *sertraline*, have been studied in autism. Fluoxetine was reported to improve 15 out of 23 adolescents and adults with autism in an open-label design (28). In a placebo-controlled study of five autistic subjects, aged 10-30 years, only one subject improved moderately in compulsive symptoms on 20-mg fluoxetine per day. Open-label results of sertraline in autism have also been promising, indicating that 24 out of 42 adults were rated as markedly improved following treatment with 50–200 mg sertraline for 12 weeks (56).

The results with the SSRIs are encouraging in adults with autism who are characterized by strong behavioural rigidity and obsessive-compulsive-like symptoms. In contrast, children and adolescents seem to be very sensitive to the stimulating side effects of SSRIs and have a much lower response rate.

Buspirone, an agonist of the serotonin $5T_{1a}$ receptor with anxiolytic and mildly antidepressant effects, has been reported only in open studies. Buspirone 5-mg t.i.d. for four weeks was given to four autistic children 9–10 years old (110). Two children showed clinical improvement, and no significant side effects were reported. Developmentally disabled adults with autism were open-label treated with buspirone in dosages of 15–45 mg/day and showed a decrease of anxiety, temper tantrums, aggression and self-injurious behaviour (106, 109). We have successfully used buspirone 15–30 mg/day as an adjuvant in the residential treatment of disorganized and hyperaroused children with autism. Positive drug responses consisted of a reduction in affective lability and a decrease in anxieties and sleeping problems (20).

Medication affecting dopaminergic neurotransmission

Of the classic neuroleptic drugs, *haloperidol* has been studied intensively concerning its effects and safety in autism. In a series of controlled investigations haloperidol in dosages of 0.25–4.0 mg per day for four weeks was significantly effective in decreasing motor stereotypies, hyperactivity, withdrawal and negativism in a group of two- to eight-year-old autistic children (4, 5). Following six months of continuation treatment haloperidol remained effective with 71.5 % of the children, but left 20 % unchanged and 8.5% worsened (95). Short-term side effects reported were dystonic reactions, acute dyskinesia, parkinsonism, akathisia, and autonomous and cardiovascular signs and symptoms. The long-term efficacy of haloperidol is not well documented, however, and the risk for serious long-term side effects such as tardive dyskinesia, induction of anxiety and depression, and weight gain is of great concern. In a prospective study of 82 autistic children treated with haloperidol 24 children were found to develop dyskinesia (21). The design of the study included a six-month period of haloperidol treatment, followed by a four-week period of placebo. In five cases tardive dyskinesia occurred, and in 19 cases withdrawal dyskinesia. All the dyskinesia symptoms disappeared spontaneously or after discontinuation of haloperidol. *Pimozide*, in doses ranging from 0.25–4 mg per day, proved to be as effective as haloperidol in a multicentre, controlled trial (91), and was found to decrease hypoactivity in autistic children (35).

The newer or "atypical" neuroleptics have received much interest over the last few years, given their lower propensity to induce extrapyramidal side effects at therapeutic doses. In addition, the positive effects of the atypical neuroleptics on the negative symptoms of schizophrenic patients seem promising as a potential strategy to improve the core social deficits of subjects with autism. Pharmacologically, these newer neuroleptics block both dopamine (D_2) as well as serotonin ($5\text{-}HT_2$) receptor systems. To the best of our knowledge, *clozapine* has not been investigated in autism. A series of open-label studies in children, adolescents and adults have documented promising clinical improvements following treatment with *risperidone* (39, 40, 52, 81, 92, 96). For example, 20 children and adolescents with a developmental disorder refractory to other psychotropic treatments were successfully treated with risperidone in dosages ranging from 1.5–10 mg/day (52). Common side effects of risperidone were weight gain and sedation. The risk for extrapyramidal side effects and tardive dyskinesia when administering risperidone is not totally absent and necessitates low dose treatment, preferentially in the range of 0.5–4.0 mg/day. In our clinical practice we recently treated two boys with autism who developed tardive dyskinesia when on risperidone. Both boys had symptoms in the oro-buccal region, which disappeared over a period of some weeks after the risperidone had been discontinued. It is further recommended

to monitor weight carefully. Occasionally, an increase of hepatic enzymes and fatty infiltration has been reported following risperidone (45, 72). NIH-sponsored, placebo-controlled, multicentre studies regarding the efficacy and safety of risperidone in children with autism are ongoing. A placebo-controlled parallel study in adults with autism and PDD-NOS indicated that risperidone in dosages from 1.0–6.0 mg/day for 12 weeks was superior to placebo in reducing irritability, aggression, repetitive and affective symptoms (82). Objective changes in social and communicative behaviour were not observed. The drug was well tolerated; the most prominent side effect was mild transient sedation.

The psychostimulants are the first-line treatment of symptoms of hyperactivity, inattentiveness and impulsivity. Since subjects with autism often are hyperactive and highly distractible, treatment with stimulants would appear an obvious strategy. Earlier studies found that *methylphenidate* worsened symptoms such as stereotypies when used in hyperactive children with autism (10, 23). A recent double blind, crossover study in 10 autistic children aged 7–11 years, using placebo and two dosages of methylphenidate (10 mg and 20 mg b.i.d.), showed that both dosages of methylphenidate resulted in a significant decrease in hyperactivity. Troublesome side effects were found to be absent, particularly the worsening of stereotypic movements (105). Negative effects of stimulants are thought to occur mostly with mentally retarded children with IQs below 45 or mental ages below 4.5 years (1).

Medication affecting the peptidergic system

Panksepp (93) hypothesised that autism was based upon a hyperfunctional endogenous opioid system, which resulted in diminished social interest. This stimulated research on the therapeutic effects of opiate antagonists in autism. The results of placebo-controlled studies in children with autism with *naltrexone*, an opiate antagonist that can be orally administered, were overall disappointing (22, 69, 70, 75, 127, 129). Though treatment with naltrexone in a dosage of about 1.0 mg kg^{-1} day^{-1} was consistently associated with a significant but modest reduction of hyperactivity, the social and communicative deficits and the stereotyped behaviours at the group level failed to ameliorate following naltrexone. Open-label continuation treatment for a period of six months of five autistic children, who showed a clear individual response to naltrexone in the four-week trial, did not reveal therapeutic effects on social and communicative functioning (126). Furthermore, in a double-blind, placebo-controlled, crossover study in mentally retarded adults with autism and/or self-injurious behaviour, naltrexone failed to affect self-injurious and autistic behaviour in a positive way (125). Naltrexone has a bitter taste, which can give rise to compliance problems. Side effects of naltrexone were mild and transient. Overall, we would not advocate naltrexone for the treatment of autism on a routine base.

Secretin is a polypeptide that is present in the so-called S cells in the mucosa of the upper small intestine in an inactive form, prosecretin. When acid chyme with pH less than 4.5 to 5.0 enters the duodenum, secretin is released into the blood. Secretin causes the pancreas to secrete large quantities of fluid that contain a high concentration of bicarbonate ion. This provides an appropriate pH in the duodenum for the digestive action of the pancreatic enzymes. An anecdotic report of a child with autism whose condition markedly improved after an open-label treatment with a single dose of secretin led to inflated claims by the media and on the internet (http://secretin.com, and http://autism.com/ari), and up to thousands of children with autism may to date have been treated by secretin injections. Some clues may be found in the neuroscience literature to provide a theoretical rationale for using secretin in autism. For example, secretin receptors are present in the hippocampus, and secretin has been further found to bind to receptors of another peptide (vasoactive intestinal peptide) in the hypothalamus, cortex and hippocampus. Next to a direct neuropeptidergic action of secretin, indirect influences may be involved as well, such as on the activity of brain neurotransmitter systems, brain circulation, or gastrointestinal permeability (58). It is important, however, that the available evidence of the claimed effects of secretin in autism was rather limited and preliminary. Limitations include small sample sizes, inadequately characterized subjects, poorly defined outcome measures and the absence of placebo-controlled and double-blind designs. Moreover, carefully conducted and controlled studies in larger samples of children with autistic spectrum disorders failed to see any benefit of a single dose of secretin (117). The results of other controlled trials that are in press seem to point in the same direction. There are several lessons to be learned from the secretin hyphae (123). Professionals should be extremely cautious in making therapeutic claims in the absence of substantial supporting data. Parents, on the other hand, may be so eager to obtain a cure for their child that they tend to pursue unproven treatments while not being well informed about both safety and efficacy, and run the risk of depleting their financial and psychosocial resources.

Medication affecting noradrenergic transmission

Two controlled studies (37) reported on the use of *clonidine*, a presynaptic a2-adrenergic receptor agonist. Clonidine was able to reduce hyperactivity, impulsivity and irritability on a short-term basis. Clinical experience, however, indicates that many patients will develop tolerance to the therapeutic effects of clonidine, which seems to limit its applicability in clinical

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practice. Reported side effects are drowsiness, decreased activity and hypotension.

In open trials *propranolol*, a lipophilic β-blocker, was used to treat aggression, self-injury and impulsivity in developmental disorders (107, 108). It is necessary to perform an ECG before starting treatment to check for pre-existing cardiac conduction anomalies, and to monitor pulse rate and blood pressure regularly because of the risk of bradycardia and hypotension. Contra-indications to using the β-blockers are, among others, comorbid diabetes mellitus, obstructive pulmonary and cardiovascular diseases.

Miscellaneous agents

When the symptoms of a child show a cyclic pattern, or when for instance a bipolar mood disorder is suspected, treatment with *lithium* can be helpful. Successful treatments in autistic patients with periodical upraise of symptomatology have been described (67, 71). Lithium can also be used in the treatment of aggressive and self-injurious behaviour in autistic subjects (15).

20; to 30 % of the children with autistic disorder suffer from epilepsy. Therefore anticonvulsants can play a role in the management of the disease. *Carbamazepine* is reported to have, in addition to an anticonvulsive effect, positive effects on mood disorders and on aggressive, irritable or explosive behaviour in autistic children (46). Open-label treatment with *valproate* also resulted in improvement in behavioural symptoms associated with autism (104).

Table 1 Clinical guidelines for pharmacotherapy in autism

Target	Medications
Hyperactivity, impulsiveness	Methylphenidate or other stimulants Atypical antipsychotics Clonidine Naltrexone
Rigidity, rituals	Selective serotonin reuptake inhibitors Atypical antipsychotics
Aggression, self-injury	Atypical antipsychotics Lithium β-Blockers Anticonvulsants Clonidine
Anxiety, affective symptoms	Buspirone Atypical antipsychotics Clonidine

Clinical recommendations

One may consider prescribing medication to subjects with autism when target symptoms such as hyperactivity, aggression and self-injury, stereotypies and rigidity, and anxieties

Table 2 Medication regimens

Medications	Dosages	Comments
Stimulants		
methylphenidate	0.3–0.7 mg/kg/d (5–60 mg/d) in 2–4 doses	Low-dose regimen; cave induction of stereotypies and of psychotic decompensation
dextroamphetamine	0.15–0.35 mg/kg/d (2.5–40 mg/d) in 2–4 doses	
Clonidine	about 4 μg/kg/d in 2–3 doses	Cave bitter taste
Naltrexone	0.5–2.0 mg/kg/d in 1–2 doses	
Atypical antipsychotics		
risperidone	0.25–3 mg/d in 1–2 doses	Low-dose regimen; cave weight gain, behavioural activation and extrapyramidal symptoms
olanzapine	2.5–15 mg/d in 1–2 doses	
Lithium	to a serum level of 0.8–1.2 mEq/L	
β-blocking agents		
propranolol	20–300 mg/d in 3–4 doses	
SSRIs		
fluvoxamine	25–300 mg/d in 1–2 doses	Low-dose regimen; cave behavioural activation
fluoxetine	5–80 mg/d in 1–2 doses	
sertraline	25–200 mg/d in 1–2 doses	
Buspirone	15–60 mg/d in 3 doses	
Anticonvulsants		
carbamazepine	to a blood level of 4–12 μg/mL	
valproate	to a blood level of 50–100 μg/mL	

interfere with psychosocial adaptation or negatively interferes with psychological and behavioural treatment approaches. For a number of these target behaviours, environmental manipulations and focused behavioural interventions may be as effective as medication (60-62). Further, incidental or episodic comorbid disorders such as depressive conditions may be a focus of pharmacotherapy. The clinician should carefully assess the risks and benefits of medications, since the database of well-performed and controlled medication studies in autism is limited and, in particular, our knowledge of long-term effectiveness and safety of drug treatment is lacunar. This should be communicated to the patient and/or his/her family in the process of obtaining informed consent. Clinical guidelines and dosages for the pharmacotherapy of autism are summarized in Tables 1 and 2. Hyperactivity and inattentiveness in a task-related context similar to that observed in attention-deficit hyperactivity disorder may be responsive to stimulant treatment, and should be differentiated from a lack of social attention associated with joint attention deficits and from being absorbed with preoccupations and interests. Clinical experience suggests that selective serotonin reuptake inhibitors are particularly effective to treat rigidity, rituals and stereotyped patterns of behaviour when interruption of these behaviours is accompanied by aggression or increased anxiety.

Conclusions

Autism is an aetiologically and clinically heterogeneous disorder, for which, as yet, no consistent neuroanatomical, neurophysiological or neurochemical abnormality has been identified. To date, internationally well-concerted efforts are being made to unravel the genetic mechanisms of autism and to localize and ultimately identify genes involved. This has the prospect of potentially documenting new biochemical pathways to normal and abnormal social and communicative behaviour. In turn, this may give new clues for the development of effective and safe medications for subjects with autism. Unfortunately, little progress has been made over the past few decades in developing new and effective pharmacotherapies for autism. Medication research in autism has evolved in the slipstream of the psychopharmacology of the major psychiatric problems of adult age rather than as a result of investigational activities well focused on the specific characters of the disorder.

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