

Medical Therapies Paper at Autism NZ 2002 National Conference

By Professor Gillberg

Medical therapies in the autistic syndrome are a subject fraught with difficulty. Accurate evaluation of medical therapies throughout medicine has its limitations because of the effects of treatments on volatile human beings. These studies are plagued by the placebo effect and a number of other possible misinterpretations due to lack of randomness, inappropriate or imprecise instrumentations, small samples or attrition of participants, statistical regression toward the mean, absence of long-term follow up etc. It is not unusual for well-designed studies from excellent medical centres to disagree with each other.

In the case of treatment studies in the behavioural syndrome of autism, there are all the usual culprits compounded by additional ones. A major extra problem is the fact that any behaviour measurement is inevitably greatly affected by what actually happens in real life each day to a child with an extraordinarily tuned sensory system. Also, that child is growing up, maturing and changing while the evaluation of the therapy is underway. Another problem is that the medicines are rarely targeted to specific diseases or identified subgroups of patients with autism; they may be tried out on any child who happens to meet a predetermined diagnostic criterion of autism. Under these circumstances, in spite of the careful research designs, with elaborate statistics, in the many studies discussed in this chapter, the results of the evaluations of medical treatments described here would probably be most accurately described as 'best guesses'.

To our knowledge there is no established medical treatment that cures any group of patients with autism. In a study in England, Grafton et al. (1998) found that it was the diagnosis of autism, rather than the specific behaviour of the child, that often led to trials of antipsychotic medication; this conclusion was reached by comparing autism with conduct disorder—which also has aggression and destructive behaviour. Tsai (1999) has written an excellent summary of psychopharmacological research and indications in autism.

There are medical therapies that are reported to be likely to improve the clinical dysfunctions of autism in particular children. These medical therapies of the autistic syndrome fall into three categories. First, wherever possible, is the ideal therapy of actually treating the basic disease process itself which is causing the symptoms of autism—targeting the specific place in the metabolic pathway, etc. A second approach to medical therapy involves treatment of symptom complexes not specific to, but found within, the autistic syndrome—such as treatment of sleep disorders or hyperactivity. These are the symptomatic treatments. Finally there are the non-specific therapies that attempt to treat the core symptoms of the overall syndrome that we call autism, when it is not further defined. In the non-specific therapies, although the drugs are classified by a particular mode of action, it needs to be noted that the full impact of each drug on the brain usually involves other metabolic pathways and is often far from being well understood.

Therapy for symptom complexes within patients who fit the criteria of an autistic syndrome; although these behaviours are not unique to autism some of them may be a troubling part of the clinical management of the person with autism.

HYPERACTIVITY/ATTENTION DEFICIT DISORDER

Children with an autistic spectrum disorder have been described with both hypoactivity and hyperactivity. The hyperactivity seen in children with autism may be part of a pattern of hyperarousal behaviours, such as hyperactivity, hypervigilance, stereotyped body movements and even self-stimulation. The distractibility and poor attention span of some of these children often compound their already serious educational problems. Methylphenidate, a commonly used drug to improve attention span, has been used in autism, other choices include clonidine and naltrexone.

Clonidine is increasingly being used to treat attention deficit/hyperactivity disorders. There are several studies of clonidine performed in patients with autism; Fankhauser et al. (1992) reported that clonidine was effective in reducing hyperactivity, hypervigilance and improving social relationships. However possible side effects; drowsiness and sedation, were noted by McCracken and Martin (1997).

SLEEP DISORDERS

A chronic sleep disorder is often a major problem both for the child with autism and the sleep-deprived parent. Traditional approaches include behavioural therapies and sedatives.

Also the histamine H1-receptor antagonist niaprazine is reported to help both the sleep disorder and behaviour problems in some people with autism. Abnormalities in circadian rhythm have been demonstrated in children with autism (more information on this in the full paper-available at Autism NZ National Office). After a child has had a complete medical work-up, which has ruled out any autoimmune disorder, melatonin is another option to consider for a child with a disturbance of chronic sleep-wake cycle (Lord 1998). An oral dose of fast-release melatonin taken at bedtime may be helpful; side effects of the development of tolerance are rare (Jan & O'Donnell 1996).

AGGRESSION

One of the most disruptive problems of individuals with autism is aggressive behaviour, historically treated by behavioural management combined with neuroleptics, anti depressants and sedating agents. Beta-blockers such as propranolol, have been used with success for aggression in some patients with autism; there is a good discussion of the mechanism of action and clinical use in a paper by Haspel (1995). Koshes and Rock (1994) have suggested the use of clonidine in an adult with intermittent explosive disorder. Hillbrand and Scott report (1995) report on the value of busipirone with aggressive behaviour.

A newer approach to controlling aggression is the use of riseridone, an atypical neuroleptic drug. Data from a double-blind, placebo-controlled study of adults with autism found that risperidone produces reductions in aggression, repetitive behaviour & affective symptoms.

An open study of eleven male out-patients with autism also showed improvements in aggression as well as explosivity, self injury and poor sleep hygiene. In a study of eight adults with mental retardation, half of whom have an autistic spectrum disorder, reduced aggression occurred with the use of risperidone.

In a study involving a single individual with autism who was part of a larger clinically heterogeneous group of retarded children and adolescents receiving risperidone, Schreier (1998) reported that the autistic child who had aggressive behaviour did not respond to the

risperidone. It was also noted that this child lacked the effective symptoms seen in the other retarded children who did not respond to the drug.

NON-SPECIFIC THERAPY FOR AUTISTIC SYMPTOMS IN GENERAL

Is there a drug which might reverse autism? Could there be a drug that would reverse some of the core symptoms of autism? It has been reported that there are no well-established medications to treat core symptoms of autism. Regarding new drugs particularly those in the serotonin class Rapin (1997) wrote that the group certainly are not curative of autism disorders.

A-TYPICAL ANTIPSYCHOTICS

The Benzisoxale derivatives are a relatively new chemical class of drugs. They are believed to act through dopamine type and serotonin type 2a receptor antagonism, as well as antagonism and other unspecified receptors (PDR 1999). An example that has been tested in patients with autism is risperidone. This drug has been reported to be superior to placebo in reducing overall behavioural symptoms of autism, as well as repetitive behaviour, aggression, anxiety, depression, irritability-in 8 out of 14 adults with autism who participated in the study over 12 weeks.

Recently there has been evidence that if risperidone is effective it may continue to be so for at least 2 years. Risperidone has been used in children as young as 23 months to improve social relatedness and reduce aggression.

Regarding side effects of risperidone, it has been reported to cause weight gain, hepatotoxicity and alas, tardive dyskinesias. However, it has also been reported to diminish the severity of tardive dyskinesia induced by other neuroleptics. A caution to keep in mind is that combining risperidone with valproate-a drug often used for seizure control in autism can result in edema. When risperidone is combined with SSRIs, enuresis has been reported.

Another a-typical antipsychotic is clozapine. This is a new and complicated drug and, studies in regard to autism are not documented for this drug.

DRUGS THAT MAY ESPECIALLY AFFECT THE SEROTONIN PATHWAY

An early study of tryptophan loading tests in patients with autism demonstrated improvement in those loading tests when the amount of vitamin B6 co-factor involved in the tryptophan metabolic pathways was increased. The hope that drugs affecting serotonin might possibly be a panacea for children with autism was enhanced when it was found that tryptophan depletion led to a significant worsening of symptoms in 65 percent of patients with autism, compared to a sham depletion. (McDougle 1996).

Since the symptoms of individuals with major depression, obsessive-compulsive disorder and panic disorder did not worsen after tryptophan depletion, the result in autism raised the possibility that serotonergic dysfunction might be more central to the pathophysiology of autism than that to other psychiatric disorders. However, since up to 99 percent of tryptophan in the body does not go down the serotonin pathway a great deal more work is needed to understand these research results and evaluate them.

At first there was considerable interest in clomipramine-a ticyclic anti-depressant with SR1 Properties, the drug is effective in suppressing obsessional behaviour, however, in spite of

promising early reports it made some children with autism worse.

At the moment there is a high level of interest in drugs which selectively and powerfully inhibit serotonin. Besides the obvious interest in that these drugs might help the core symptoms of autism, this has not been proven and, in fact in many cases it has worsened the symptoms. One symptom of autism though that is most disabling to families is a child's intolerance to change in routine and environment. It is reported that in 8 out of 9 people with autism it helped them cope better with transition, and there were minimal side effects.

Fluoxetine the SRI drug being tested was subject to open trial. It was reported that it led to a significant improvement in 15 out of 23 subjects with autism. But, 6 out of 15 developed side-effects which interfered with their function.

There are however single case studies showing dramatic improvement in certain adults and children with autism. For further information and details, please contact Autism NZ.

IMMUNOTHERAPIES

In view of the evidence of immune dysfunction in some children with autism the possibility of some kind of immune therapy in the future has been raised (see Chapter 13.) Nothing has yet been established although there is evidence for infection-triggered tics & OCD in children.

VITAMINS

Vitamins-specifically pyridoxine (vitamin B6) and ascorbic acid-have been tried as therapy in patients with autism. In an open trial Heeley and Roberts reported that pyridoxine improved a tryptophan loading test in children with autism. In one trial by Rimland (1974) a subgroup of children with autism appeared to respond to pyridoxine, relapse on withdrawal, and respond again when re-started. All tests were inconclusive as people were chosen for certain reasons, not picked at random.

The Lelord group in France (1978) added magnesium to their protocols and found this ineffective. It should also be noted that when given over a long term period that pyridoxine may cause side effects.

PROBLEMS WITH SIDE EFFECTS OF DRUGS

Tardive dyskinesia, an involuntary abnormal movement disorder is a serious untoward effect of some drugs used in autism, particularly those classified as dopamine-receptor blockers. Some patients with autism who receive long term neuroleptic medicines develop what appears to be Tourette Syndrome when withdrawn from neuroleptics. In some cases it is hard to be exactly sure what happens. (There can be severe side effects for some).

Occasionally pharmaceuticals used in autism can cause a most serious problem-neuroleptic malignant syndrome (NMS). The three major manifestations of NMS are fever, rigidity and elevated CK levels. Additional characteristic symptoms include tachycardia, tachypnea, altered consciousness and leukocytosis. Fatalities have been reported.

PROPOSED NEW THERAPIES

When one compares the medical therapies proposed in the second edition printed in 1992, it is of interest that many of the drugs described in this chapter and in this the third edition (2000) are newly described. The turnover is great over an eight year period. This is a sign of a

struggling field of medicine without final answers. Thus, it is vital to remain open to new concepts and theoretical proposals regarding pharmacotherapy in autism. One such proposal by a major researcher (Carlsson 1998) has suggested the use of glutamate agonists. It will be fascinating to see what the future brings.

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