The Use of Medication for People with Autism Spectrum Disorders

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"Charter of Rights for Persons with Autism (accepted as a written declaration by the European Parliament, May 6th 1996)
No 18 THE RIGHT of people with autism to freedom from pharmacological abuse or misuse."

Studies from the graves of our prehistoric ancestors indicate that drugs have been used in an attempt to cure disorders or minimise suffering from the earliest of times. Waltz & Shattock (2004) reported on records, stored at London's Great Ormond Street Hospital, which showed that drugs were being used in an attempt to help people recognised as possibly suffering from autism over a century ago. Some of these attempts we would recognise as having possible benefits (cod liver oil, senna, and bromides, for example) but others (such as calomel) we would now recognise as being misguided.

Such regimes were based upon state-of-the-art principles as they were understood at the time. They consisted of using whatever therapies were available and which experience with other conditions had indicated could be beneficial. Very little has changed. Medications used by physicians for people with autism tend to be based upon experience with other (related or unrelated) disorders, lateral thinking and serendipity. The plethora of substances used in complementary medicine confuses the issue further. Practitioners of complementary medicine, such as those involved with DAN! (Defeat Autism Now!) are attempting to assess and evaluate such therapies but the situation, with regard to efficacy and safety, is still very unclear.

Interventions used by complementary practitioners tend to rely upon attempts to interfere with the biological mechanisms that may underlie autism. Usually, these

interventions consist of manipulations of diet or supplementation with vitamins, minerals and other normal elements of metabolism. Orthodox medical practitioners utilise synthetic drugs that have a potential for side-effects in proportion to their very high pharmacological activity.

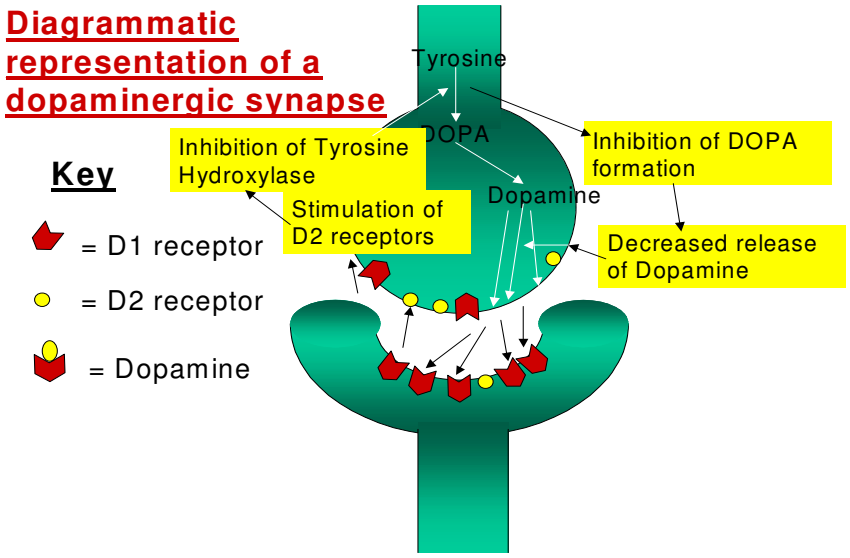
When used with care and with appropriate monitoring there is no doubt that such drugs can greatly increase the quality of life for the person with an ASD as well as their carers. On the whole, medication tends to be used against specific target symptoms such as epilepsy, hyperactivity, stereotypic behaviours rather than targeting core autistic features. A discussion of the indications for and usefulness of these medications is beyond the scope of this presentation. We can do no better than refer you to specific texts such as those by Santosh & Baird (1999; 2001), Berney (2000) and Barnard *et al* (2002).

Theoretical Model

We have described a theoretic model based upon "*opioid excess*" theories on a number of occasions (Shattock *et al*, 1990; Shattock & Lowdon, 1991; Shattock & Whiteley, 2002). However, it is not necessary to subscribe to the more contentious aspects of possible involvement of opioid peptides in autism to accept the main tenets of the hypothesis that are of relevance to this discussion on medication.

There are many subtypes of dopamine and serotonin receptors. The clinical significance of some of these subtypes has yet to be determined. However, the basic principles are the same at all synaptic junctions so one example will serve to illustrate the principle that will apply in all situations. The synapse diagram shown below (Figure 1) represents the situation that would be seen in a synapse within the nigrostriatal (dopaminergic) system in the Central Nervous System.

Figure 1.



As the predominantly presynaptic D_2 receptors are stimulated by dopamine or possibly by opioid peptides, there will be a decrease in the amount of dopamine released from the presynaptic terminal, a consequent reduction in the stimulation of the postsynaptic D_1 receptors and, therefore, a reduction in transmission along this system. The mechanism appears to be designed to "autoregulate" transmission when excessive stimulation occurs.

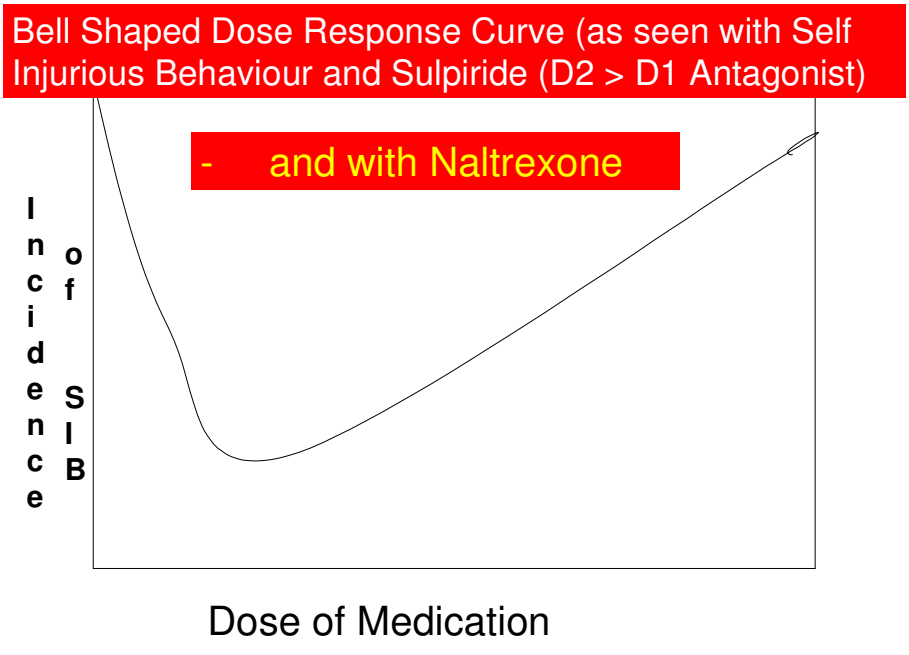
The *opioid-excess* theories require that elevated levels of opioids, whether naturally occurring such as the endorphins and enkephalins or of exogenously derivation such as the casomorphins (from dietary milk) or gliadinorphins (from dietary wheat) stimulate these D_2 receptors and effectively dampen down transmission in this system. It is worth pointing out that in some dopaminergic systems, such as the mesolimbic systems, the D_2 receptors are found post-synaptically . Stimulation of these receptors would result in elevated transmission and the occurrence of stereotypic behaviours. Thus the same compound could result in stimulation of one of these systems whilst inhibiting another.

The Newer "Atypical" Neuroleptic Drugs

Antipsychotic medications such as haloperidol and sulpiride were known to exert their inhibitory effects preferentially against the D_2 receptors but as the concentration increased there would be inhibition of the D_1 receptors. The effect (in the nigrostriatal system at least) would be an initial increase in dopaminergic transmission. As the dosage increased, however, there would be a diminution of transmission.

The consequence would be, in clinical terms, a bell-shaped dose response curve. This is what was seen when, for example, the incidence of self injurious behaviour was plotted, graphically, against the levels of sulpiride (Busse, 1988) Similar trends were also seen with the antiopioid drug, naltrexone (Campbell, 1988).

Figure 2.



Thus, at lower doses there was an inhibition of the target behaviour but at higher doses this effect disappeared and, in fact, may even have been exacerbated.

The newer antipsychotic drugs such as risperidone, olanzepine and quatiepine are somewhat "cleaner" than haloperidol and sulpiride. At the time of introduction to the market it was alleged that they would be without the serious side-effects (dyskinesias and extrapyramidal effects) that limit the usefulness of the older drugs. Experience suggests that although the incidence of such side effects is, indeed, diminished, risks remain and other serious side-effects may have emerged (Barnard *et al* 2002).

One major "bonus" with these drugs is that as well as inhibiting the presynaptic (D_2) receptors they will inhibit uptake by the presynaptic receptors for the serotonin pathways – the $5HT_2$ receptors. Theoretically there should be resultant increases in transmission in the serotonergic system and consequent improvements in mood, temperament and aggressive episodes.

At the same time there are undeniable reports of substantial and unacceptable weight gains in people, with ASDs, using these medications and there may be a heightened risk of development of diabetes. Given this potential for harm, it would seem to be appropriate for anyone taking these medications for a prolonged period to be tested for diabetes on a regular basis.

Specifically Serotonin

There have been many reports, over the years, of elevated levels of serotonin in the blood of people with autism. Many have questioned the significance of this finding on the basis that serotonaemia is likely to be reflective of intestinal sources rather than of CNS origin. The assumption was made that this indicated hyperserotonergic activity in the neuronal system but this appeared to be at odds with other observations. The more recent findings of Pederson *et al* (1999) of selective serotonin uptake stimulating peptides in the urine of people with autism would suggest that serotonin is likely to be found in the platelets of the blood rather than in the serum. This finding was recently confirmed by Mulder *et al* (2004). Observations in the platelets are usually regarded as representative of what happens in neuronal terminals so elevated levels in the platelets would indicate reduced serotonergic transmission in the CNS.

Additionally, our own findings of elevated levels of *trans*-indolyl-3-acryloylglycine (IAG) (Bull *et al*, 2003) in the urine of people with ASDs would also indicate abnormalities in this system. This would suggest a possible deficit of overall levels of serotonin since the formation of serotonin from tryptophan would be distorted towards IAG (Anderson *et al*, 2002). Accordingly, medications that restore serotonergic transmission (Risperidone and other atypical neuroleptics and the Selective Serotonin Uptake Inhibitors or SSRI drugs) would be helpful in some people with ASDs. In fact, it appears that the SSRIs are helpful for many of the higher functioning population people with ASDs, especially where depression and anxiety may be involved, but our experience is that they are of little benefit for those subjects where the problems are more severe.

Supportive data for the use of the atypical neuroleptics is virtually absent. After these drugs had been in regular use for many years, a trial did demonstrate efficacy in some people with ASDs. Again, there would appear to be an optimal dose range and we must presume that the explanation is similar to that shown with sulpiride (Figure 2).

Confusion of Autism Spectrum Disorders with Schizophrenic Disorders

It is accepted that in schizophrenic syndromes there is excessive dopaminergic transmission. The neuroleptic drugs used in autism were developed for treating schizophrenia and were tried for people with autism because there was little else around. They acted as general depressants appearing to calm the subject down and make them easier to manage. It was doubtful whether there were any effects on the primary symptoms of autism. The terms "*liquid cosh*" and "*chemical straightjacket*" have been applied to such situations by mental health service users and advocates in recognition of the fact that lives that were, which were, in any case, unhappy have been more or less destroyed through such misuse. Such abuse should have been consigned to history long ago but we are hearing worrying reports of its unintentional reappearance.

In the early days of autism research there was considerable confusion about the existence of a relationship with schizophrenia. Indeed, autism was often referred

to as “childhood schizophrenia” in early literature. However, the differences between the historical development and the clinical manifestations of autism spectrum disorders and schizophrenia are so profound as to make confusion difficult for current practitioners. The fundamental differences, but not the only ones, are that autism spectrum disorders typically begin in very early childhood and are characterised by pervasive, multi-system developmental effects. Although current research indicates that people diagnosed with schizophrenia in adulthood may be characterised as having a developmental history that deviates from the norm, the developmental precursors observed are subtle and not significant enough to be predictive (Isohanni *et al* 2004). They certainly do not resemble the well-established patterns associated with ASDs.

For reasons of privacy of information, we are unable to describe particular cases but it is becoming increasingly apparent that some people who had been diagnosed with Asperger syndrome or high functioning autism are being re-diagnosed, when they reach adulthood, as schizophrenic.

Diagnosis is helpful only if it leads to appropriate intervention and treatment - and this re-diagnosis has profound implications for treatment particularly in terms of medication. Drugs have a considerable role to play in the treatment of people with schizophrenia. The drugs commonly prescribed are those that are used for ASDs but in very much higher doses.

In a typical scenario, a young man with Asperger syndrome is re-diagnosed as having Schizophrenia. He is then given drugs in levels much higher than are appropriate. He does not respond appropriately and so the dose is increased further and further until it reaches a level where it would be dangerous to even attempt to reduce or remove the medication. This scenario has been played out many times over the past few years. Sometimes the person is sectioned and all contact with the (worrisome and annoying) parents is stopped. There is no appeal and no publicity is allowed. “*The rights of the individual who has been sectioned would be infringed if publicity is obtained*” seems to be the line taken by the English and Scottish courts.

Misdiagnosis is one reason for inappropriate medication levels but there are others, which can result from not appreciating the particular requirements of ASDs.

Testing of Drugs

As indicated before, there have been very few good quality trials on drugs for adults with ASDs and virtually none for children. Trial design has generally not met the randomised, double-blind, cross-over "*gold standard*". Most trials have followed very few participants and often essential baseline data on participants was not established to ensure that a reasonably homogenous population was chosen (for example the absence of seizure disorders, immune system dysfunction and other etiological factors has rarely been determined when population samples of individuals with ASDs were chosen). Consequently we know very little about how individuals with ASDs will be affected by medications that are now in common use. Trials of these medications have been conducted on people with schizophrenia, depression obsessive-compulsive disorder or hyperactivity. The assumption is made that the effects and the metabolic handling will be the same in people with ASDs. This assumption is unjustified and in some cases demonstrably wrong.

It is strange that when dosages are being considered, allowances are made for age, sex, size and, on occasions, race but no allowance is made for people with ASDs when it has long been known that, in these individuals, the processes that control metabolism and removal of drugs from the system are, almost universally, impaired.

It is now some years since Waring *et al* (1996, 2000) demonstrated that systems relating to sulphation and sulfoxidation will be impaired in people with ASDs because of a deficit in plasma sulphate ions. Similar results were shown by an Italian research group (Alberti *et al*, 1999). Waring performed other studies which demonstrated that metabolism of paracetamol would be impaired under such circumstances. Deth & Waly (2003) and James (2003) have also demonstrated clear deficiencies in methylation systems in people with ASDs compared to controls. Thus, any drug reliant upon either or both of these mechanisms will persist for very much longer in the bodies of people with ASDs than in control populations. Such knowledge and understanding does not preclude the use of such medications in subjects with ASDs but it does indicate a requirement for great care in the introduction of such interventions and for vigilance in the form of constant monitoring over a prolonged period of time.

As a rule of thumb it is usual to assume that when medications are given on a regular basis it will take 5 times the half-life for a drug to reach its maximal level. As this stage is reached, the rate of breakdown will equal the rate of introduction and a more or less constant level will be maintained. Where, on account of reduced catabolism, the drug (and perhaps its active metabolites) are more persistent in the body, there will be a greatly increased time before this constant level is reached and this level will also be much higher than would otherwise be the case. In the same way, clearance will take considerably longer than in control populations.

We are aware that some physicians are successfully employing what would appear to be very low doses of medication to control epilepsy (20mg of Carbemazepine twice a day for example) in people with ASDs. We have also observed dramatic effectiveness of very low doses of naltrexone. There is considerable scope for experimentation with very low doses of many other drugs.

Other, as yet unexplored mechanisms may also apply. For example, recent research linking altered immune function with unusual opioid receptor activity (Hutchinson *et al* 2004) could have profound implications for the use of certain medications in people with ASDs.

Conclusions

Drugs can be useful in controlling some of the more troublesome symptoms seen in individuals with autism but there has been insufficient research on the doses required for people with ASDs and, on the whole, results have been disappointing. Anecdotal evidence and some research indicates that doses required for people with ASDs are considerably lower than those for people with schizophrenia so precise diagnosis is very important. People with ASDs have underlying problems with sulphation and methylation, so any drug using these mechanisms in their metabolism would build up within the subject. In order to avoid potentially very serious over-dosages, unusually low doses may, be appropriate for people with ASD. Rigorous research will be required to determine appropriate dosage levels for this population.

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