

Pharmacological Prescribing in Autism



Off-label prescribing, study bias & safety

Conventional pharmacological management in Autism Spectrum Disorders (ASD) has targeted dysfunctional behavioural symptoms that interfere with behavioural therapy efforts or deal with issues such as aggression, irritability, stereotyped behaviours, anxiety, hyperactivity, and sleep difficulties. Doctors in wealthy countries such as Belgium, Switzerland and Australia prescribe more medications to people with autism than do doctors in poorer countries, including

Egypt, Pakistan and Indonesia. The most prescribed drug is risperidone, an antipsychotic that decreases hyperactivity and repetitive behaviour. Doctors also prescribe **off-label** antidepressants and antiepileptic drugs in high numbers to people with autism. Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group. Off-label prescribing is entirely legal and very common and isn't necessarily bad.

Unfortunately few patients, or parents are aware that they are receiving a drug off-label, and doctors are not required to tell a patient that a drug is being used off-label. New drugs are often not tested for safety and efficacy specifically in children, and even when they are tested, the results of these trials may not be disseminated to doctors. **A 2009 study found that 62% of U.S. paediatric office visits included off-label prescribing, with younger children at higher risk of receiving off-label prescriptions.** Specialist physicians also prescribed off-label more frequently than general paediatricians.

Off-label prescribing to children in the United States outpatient setting. Alicia Bazzano MD MPH; Rita Mangione-Smith MD; Matthias Schonlau PhD; Marika Suttrop MS; Robert Brook MD ScD (2009). Ambulatory Pediatrics 2009, 9: 81–8. [doi:10.1016/j.acap.2008.11.010](https://doi.org/10.1016/j.acap.2008.11.010).

Prozac Isn't The Same In A Kid's Body. Day to Day (2008-10-22).

It is acknowledged that there are children whose behaviour is such, that they require medication to make their lives and their families lives bearable. There is no objection to the use of pharmaceutical drugs in ASD children, so long as the child has been properly evaluated for other underlying medical conditions, biomedical markers and dietary intolerances that may be contributing to the child's behaviour, and is seen as a last option.

It is difficult to understand why the prescription of off-label medications by doctors, with little evidence of benefit, or long term safety is acceptable, whereas the use of special diets and supplements by parents is often criticised as having "no evidence" base and considered "dangerous". Surely a low-risk option should be considered first. The Autism Research Institute survey of over 26,000 parents since 1967, has consistently shown that special diets and biomedical non-drug supplements have a superior benefit to risk ratio. www.autism.com/treatment_ratings_asd

Study questions whether ASD children should be assessed for gastrointestinal co-morbidities.

A recent article, questions whether drug research trials should assess ASD children and adults for gastrointestinal symptoms. It is now being acknowledged that gastrointestinal symptoms can affect drug absorption and availability, thus having an impact on the outcome of the trials. Drug researchers are beginning to accept the need to identify subgroups of ASD children who respond well to specific treatments, something which has been widely practiced by some parents and doctors within the autism community for many years.

Should clinical trial research of psychotropic medication in autism control for gastrointestinal symptoms? Heitzer AM1, Job MA, Pandit NK, Valdivinos MG. J Clin Pharmacol. 2014 May 1. doi: 10.1002/jcph.324. [Epub ahead of print]

Changing the
way we think
about treating
autism.

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Some of the pharmacological drugs used in ASD include:

- ADHD Medications
- Antipsychotics
- Antidepressants
- α_2 adrenergic agonists
- Corticosteroids
- Naltrexone

As ASD causes substantial impairment, parents of children with the condition are motivated to try treatments regardless of the evidence. Nevertheless, it is important that prescribing clinicians are explicit to parents and patients about the limited evidence, discuss the risks of treatment, and discuss other pharmacological and non-pharmacological interventions. For example, children and adolescents with ASD appear to experience significant side effects on antidepressants, such as behavioural activation (hyperactivity and agitation), aggression, and suicidal ideation, all of which can limit their use.

Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD004677.

What's in the pipeline? Drugs in development for autism spectrum disorder. *Neuropsychiatric Disease and Treatment* 2014;10 371–381.

Studies evaluating the side effects of pharmaceutical medications only follow patients for relatively short periods of time. There are no studies that evaluate the long term effects of these medications in children.

Long term antipsychotic use in adult schizophrenia patients

“Viewed together with data from animal studies, our study suggests that **antipsychotics have a subtle but measurable influence on brain tissue loss over time, suggesting the importance of careful risk-benefit review of dosage and duration of treatment as well as their off-label use.**”

Long-term Antipsychotic Treatment and Brain Volumes: A Longitudinal Study of First-Episode Schizophrenia. Beng-Choon Ho, Nancy C. Andreasen, Steven Ziebell, Ronald Pierson, and Vincent Magnotta. *Arch Gen Psychiatry*. 2011 February ; 68(2): 128–137

Children's brains develop rapidly, so the question to ask is, what are these medications doing long term that may be interfering with the development of children's brains? The answer is we do not know!



A recent review of pharmacologic treatment in ASD reported a significant publication bias (ie, trials with positive results were more likely to be published). They found that although there was a significant treatment effect of SSRI (used for treating repetitive behaviours in ASD), these findings did not persist after they statistically adjusted for the publication bias.

Carrasco M, Volkmar FR, Bloch MH. Pharmacologic treatment of repetitive behaviors in autism spectrum disorders: evidence of publication bias. *Pediatrics*. 2012;129(5):e1301–e1310.

Unintentional Exposures

“Unfortunately, the rise in pediatric clonidine use has been accompanied by an increase in the number of unintentional exposures. In an article to be published (in print) in *The Journal of Pediatrics*, Wang and colleagues reviewed exposures to α_2 -adrenergic agonists (clonidine, guanfacine, and tizanidine) in children 12 years of age and older that had been reported to the National Poison Data System (NPDS) between January 2000 and December 2011. **There were 27,825 clonidine, 6,143 guanfacine, and 856 tizanidine exposures, with a significant increase in cases reported over time (a 5.9% increase per year).** For all three drugs, the patients were predominantly male, with a median age of 2 to 6 years. Clonidine exposure resulted in central nervous symptoms in 45.3% of patients, bradycardia in 10.2%, hypotension in 8.5%, and respiratory compromise in 2.9%. **There were seven cardiac arrests and three deaths, all associated with clonidine.** The deaths included accidental ingestions with aspiration and a compounding error resulting in an overdose. These cases underscore the need for educating families about safe medication storage and highlight the risks of compounding liquid preparations.”

Source: Advanced Pharmacotherapy Evidenced by Pathogenesis of Autism Spectrum Disorder. Yeon Jung Lee, Soo Hyun Oh, Chanmin Park, Minha Hong, Ah Rah Lee, Hee Jeong Yoo, Chan Young Shin, Keun-Ah Cheon, Geon Ho Bahn. *Clinical Psychopharmacology and Neuroscience* 2014;12(1):19-30