Biomedical Interventions for Teens and Young Adults: the Value of Persistence
(http://www.autismone.org/uploads/2006/Bradstreet%20Jeffrey%20adolescence.ppt)

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Visiting Professor of Neuroscience, SCNM
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Guiding the Biomedical Recovery Efforts: Investigate Each Child Based on History, PE & the Medical Literature
REGARDLESS of AGE

Concerns – Endless Questions
• When does brain plasticity end?
• Ongoing Immune Dysfunction
• Progress CNS Inflammation?
• Does Detox Still Help?
• Are Biomedical Interventions Still Necessary?
• Long term effects of neuropsych meds?
• Puberty, Menses, Sexuality?
• Stress, Depression, Isolation?

Encouragement
• Oldest individual to start biomedical intervention at ICDRC was 42 at the start of treatment.
• We saw significant gains in eye contact, social engagement, sleep and reductions in negative behaviors.
• Responded to IVIG and antifungals even at this age.
Magnesium VitB6 intake reduces central nervous system hyperexcitability in children.
Mousain-Bosc M, Roche M, Rapin J, Bali JP.
Department of Pediatry, CHU Nimes, 30029 Nimes Cedex, France.

CONCLUSION: This open study indicates that hyperexcitable children have low ERC-Mg with normal serum Mg(2+) values, and that Mg(2+)/vitamin B6 supplementation can restore normal ERC-Mg levels and improve their abnormal behavior.

Magnesium profile in autism.
Strambi M, Longini M, Hayek J, Berni S, Macucci F, Scalacci F, Vezzosi P.
Department of Paediatrics, Obstetrics and Reproductive Medicine, Section of Neonatology and Preventive Paediatrics, Azienda Universitaria Ospedaliera Senese, Policlinico Le Scotte, Siena, Italy. strambi@umisit.it

The aim of the present study was to determine and compare plasma and erythrocyte concentrations of
magnesium in 12 autistic children (10 boys, 2 girls), 17 children with other autistic spectrum disorders (14 boys, 3 girls), 5 girls with classic Rett syndrome, and 14 normal children (7 boys, 7 girls) of the same age. No differences in intracellular Mg were found between controls and pathological subjects; however, autistic children and children with other autistic spectrum disorders had significantly lower plasma concentrations of Mg than normal subjects (p=0.013 and p=0.02, respectively). Although our study population was small, we conclude that children with autistic spectrum disorders require special dietary management. If these cases are diagnosed at an early stage, they can be helped through diet.

Movement-related potentials in high-functioning autism and Asperger's disorder.


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nico.reinhart@med.monash.edu.au

Autism and Asperger's disorder (AD) are neurodevelopmental conditions that affect cognitive and social-communicative function. Using a movement-related potential (MRP) paradigm, we investigated the clinical and neurobiological issue of 'disorder separateness' versus 'disorder variance' in autism and AD. This paradigm has been used to assess basal ganglia/supplementary motor functioning in Parkinson's disease. Three groups (high functioning autism [HFA]; 16 males, 1 female; mean age 12y 5mo [SD 4y 4mo]; AD: 11 males, 2 females; mean age 13y 5mo [SD 3y 8mo]; comparison group: 13 males, 8 females; mean age 13y 10mo [SD 3y 11mo]) completed a cued motor task during electroencephalogram recording of MRPs. The HFA group showed reduced peak amplitude at Cz, indicating less activity over the supplementary motor area during movement preparation. Although an overall significant between-group effect was found for early slope and peak amplitude, sub-analysis revealed that the group with AD did not differ significantly from either group. However, it is suggested that autism and AD may be dissociated on the basis of brain-behaviour correlations of IQ with specific neurobiological measures. The overlap between MRP traces for autism and Parkinson's disease suggests that the neurobiological wiring of motor functioning in autism may bypass the supplementary motor area/primary motor cortex pathway.

Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005.


Department of Neurology, Rosalind Franklin University of Health Sciences, Chicago Medical School, North Chicago, IL, USA. mcchezmd@sbcglobal.net

Autism spectrum disorders (ASDs) affect 1 in 166 births. Although electroencephalogram (EEG) abnormalities and clinical seizures may play a role in ASDs, the exact frequency of EEG abnormalities in an ASD population that has not had clinical seizures or prior abnormal EEGs is unknown. There is no current consensus on whether treatment of EEG abnormalities may influence development. This retrospective review of 24-hour ambulatory digital EEG data collected from 889 ASD patients presenting between 1996 and 2005 (with no known genetic conditions, brain malformations, prior medications, or clinical seizures) shows that 540 of 889 (60.7%) subjects had abnormal EEG epileptiform activity in sleep with no difference based on clinical regression. The most frequent sites of epileptiform abnormalities were localized over the right temporal region. Of 176 patients
treated with valproic acid, 80 normalized on EEG and 30 more showed EEG improvement compared with the first EEG (average of 10.1 months to repeat EEG).

**Safety issues with drug therapies for autism spectrum disorders**


McCracken JT.

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Although currently no medication has been approved to treat autism spectrum disorders, survey data show that community practitioners are prescribing a broad range of medication treatments, including, but not limited to, antidepressants, stimulants, antipsychotics, alpha agonists, and anticonvulsants. Patients with autism spectrum disorders are also taking alternative treatments, including herbal remedies, immunologic treatments, and vitamin therapies, which may themselves produce side effects and/or create drug interactions with traditional medications. Although short-term data on the efficacy and safety of commonly prescribed treatments for autism spectrum disorders are increasing, few data are currently available on long-term treatment for autism spectrum disorders, but available studies and clinical experience can offer preliminary recommendations on the safety of and monitoring needs for the medications currently used for these disorders. Monitoring the safety and tolerability of drugs used in patients with these disorders should minimize the burden of side effects and optimize treatment outcome.

**Acute and long-term safety and tolerability of risperidone in children with autism.**


The Nisonger Center, Ohio State University, Columbus, Ohio 43210-1296, USA. aman.1@osu.edu

Treatment-emergent adverse events (AEs) were monitored during an 8-week, double-blind, placebo-controlled trial of risperidone (0.5-3.5 mg/day) in 101 children and adolescents with a lifetime diagnosis of autistic disorder. During the 8-week acute trial, the most common AEs on the Side Effects Review, scored as moderate or higher, were as follows (placebo and risperidone, respectively): Somnolence (12% and 37%), enuresis (29% and 33%), excessive appetite (10% and 33%), rhinitis (8% and 16%), difficulty waking (8% and 12%), and constipation (12% and 10%). "Difficulty falling asleep" and anxiety actually favored the risperidone condition at statistically significant levels. The same AEs tended to recur through 6 months of treatment, although often at reduced levels. Using Centers for Disease Control (CDC) standardized scores, both weight and body mass index (BMI) increased with risperidone during the acute trial (0.5 and 0.6 SDs, respectively, for risperidone; 0.0 and 0.1 SDs, respectively, for placebo) and into open-label extension (0.19 and 0.16 SDs, respectively), although the amount of gain decelerated with time. Extrapyramidal symptoms, as assessed by the SARS, were no more common for drug than placebo, although drooling was reported more often in the risperidone group. There were no differences between groups on the AIMS. Two subjects had seizures (one taking placebo), but these were considered unrelated to active drug. Most AEs were mild to moderate and failed to interfere with therapeutic changes; there were no unanticipated AEs. The side effects of most concern were somnolence and weight gain.

**Post-traumatic stress disorder in young people with intellectual disability.**

BACKGROUND: Post-traumatic stress disorder (PTSD) is common and treatable. There is extensive research on people of average intelligence yet little on individuals with developmental disabilities. METHODS: We report two people with intellectual disability (ID) who experienced PTSD. The relevance of their developmental difficulties, social and communication profiles, attentional skills, and causes of these, to their presentations is discussed. RESULTS: Both individuals have fragile X syndrome and severe ID. One has Diagnostic and Statistical Manual - 4th Edition (DSM-IV) autistic disorder; the other DSM-IV attention deficit-hyperactivity disorder. They experienced developmental and psychological regressions, new challenging behaviours and exacerbations of existing ones coincident with emotional trauma. PTSD symptoms and phenomena were identifiable despite intellectual and communicatory impairments. CONCLUSION: Presentation of PTSD is influenced by degree and cause of ID, social circumstances, social and communicatory skills, nature and timing of traumatic experience and subsequent management. The paucity of literature suggests it is missed frequently in individuals with ID who risk having problems misattributed to other causes with potential for inappropriate interventions.

Treatment incidence and patterns in children and adolescents with autism spectrum disorders.

Witwer A, Lecavalier L.

This study examined the treatment rates and patterns in children and adolescents with autism spectrum disorders (ASDs). Data were collected on 353 nonreferred children and adolescents (mean age 9.5 +/- 3.9 years; range 3-21 years) with ASDs from public schools across Ohio. Parents provided information on the use of psychotropic medicines, vitamins, supplements, and modified diets. They also completed measures of social competence, problem behavior, and adaptive behavior. Results indicated that 46.7% of subjects had taken at least one psychotropic medication in the past year. In addition, 17.3% of subjects had taken some type of specially formulated vitamin or supplement, 15.5% were on a modified diet, 11.9% had some combination of psychotropic medication and an alternative treatment, and 4.8% had taken an anticonvulsant. Logistic regressions indicated that greater age, lower adaptive skills and social competence, and higher levels of problem behavior were associated with greater medication use. This was the first study to focus exclusively on a younger population, to survey patterns of modified diets, and to obtain standardized ratings of social competence, problem behaviors, and adaptive behavior in relation to medication use. The results of this study highlight the need for more research on psychotropic medication in children and adolescents with ASDs.

Symptoms of ADHD and their correlates in children with intellectual disabilities.


Existing research suggests that children with intellectual disabilities are at increased risk for ADHD, and that the symptoms of the disorder might successfully be treated with stimulant drugs. However, there has been little
exploration of ADHD symptoms and their correlates in children with intellectual disabilities. Analyses of three samples of children with intellectual disabilities are presented (total N=338). Correlational analyses showed that younger children, and those with a diagnosis of Autism were rated as having more ADHD/hyperactivity symptoms. There was little evidence of a sex difference, and no strong associations with domains of adaptive behavior (socialization, communication, and daily living skills). However, there was a small but significant negative association between mental age and ratings of symptoms. Finally, an increased prevalence of ADHD/hyperactivity symptoms was confirmed in the children with intellectual disabilities compared to their siblings. This effect remained after controlling for chronological and mental age differences between the siblings. These findings support those from previous research and suggest that ADHD/Hyperkinesis may be a valid psychiatric diagnosis for children with intellectual disabilities. However, a great deal more research is needed to explore the phenomenology of ADHD in intellectual disability and to develop an evidence base for psychosocial intervention.

**Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder.**


_Tordjman S, Anderson GM, Pichard N, Charbuy H, Touitou Y._

Center for Scientific Research, Unite de Recherche Mixte 7593, Vurnerabilite, Adaptation et Psychopathologie, Hopital Pitie-Salpetriere, Rennes, France. lubart@idf.ext.jussieu.fr

BACKGROUND: Many studies in autistic disorder report sleep problems and altered circadian rhythms, suggesting abnormalities in melatonin physiology. Additionally, melatonin, a pineal gland hormone produced from serotonin, is of special interest in autistic disorder given reported alterations in central and peripheral serotonin neurobiology. METHODS: Nocturnal urinary excretion of 6-sulphatoxymelatonin was measured by radioimmunoassay in groups of children and adolescents with autistic disorder (n = 49) and normal control individuals (n = 88) matched on age, sex, and Tanner stage of puberty. RESULTS: Nocturnal 6-sulphatoxymelatonin excretion rate was significantly and substantially lower in patients with autism than in normal controls (mean +/- SEM, .75 +/- .11 vs. 1.80 +/- .17 microg/hr, p =.0001), and was significantly negatively correlated with severity of autistic impairments in verbal communication and play (p < .05). CONCLUSIONS: These findings indicate clearly that nocturnal production of melatonin is reduced in autism. Further research is warranted in order to understand the mechanisms underlying the lower melatonin production, to assess the impact of altered melatonin on the pathophysiology and behavioral expression of autistic disorder, and to determine the utility of melatonin administration in individuals with autism.

**Plasma androgens in autism.**


Department of Psychiatry, Universite de Paris-Sud, France.

Plasma levels of testosterone and the adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) were measured in male autistic subjects (31 prepubertal, 8 postpubertal), mentally retarded/cognitively impaired subjects (MR, 12 prepubertal), and normal control subjects (NC, 10 prepubertal, 11 postpubertal). Mean levels of plasma testosterone were similar in the postpubertal autistic (4.54 +/- 1.12 ng/ml) and postpubertal NC (5.02 +/- 1.87 ng/ml) groups. Plasma DHEA-S levels in postpubertal autistic (2170 +/- 1020 ng/ml) and postpubertal NC (1850 +/- 777 ng/ml) groups also were not significantly different. Similarly, no significant group differences were seen for testosterone or DHEA-S in the prepubertal autistic, MR, or NC individuals, although
prépubertal MR individuals with cerebral palsy did have increased plasma DHEA-S levels compared to age-matched MR or NC individuals. Significant negative correlations were found between testosterone and whole blood serotonin (5-HT) levels in the combined (all subjects, all ages) groups and in the autistic group, suggesting that the effect of puberty on whole blood 5-HT may deserve further study. Data indicate that altered secretion of the androgens is not a common feature of autism. However, abnormalities of adrenal androgen secretion may be present in individuals with cerebral palsy.

**Sexual Behaviors in Autism: Problems of Definition and Management**
George M. Realmuto and Lisa A. Ruble
*Journal of Autism and Developmental Disorders*
Issue: Volume 29, Number 2 April 1999 121 - 127
Division of Child and Adolescent Psychiatry, University of Minnesota, University of Minnesota Health Center, Minneapolis, Minnesota, 55455; Department of Pediatrics, University of Louisville, Louisville, Kentucky

Abstract  Surveys of sexual behavior in autism suggest a variety of behavioral expression. However, the course of sexual development in autism is unplotted, leaving questions about the normalcy of specific behaviors. Even less is known about deviations of sexual development and the incidence of paraphilias in this population. We explore the problems of definition of sexual behaviors and describe a case report that highlights the difficulties of management. An application of a testosterone-suppressing medication and its effect on sexual behavior are reported. After failure of behavioral and educational programs, leuprolide, an injectable antiandrogen, resulted in suppression of behaviors and retention of the participants' community placement. Follow-up for almost 3 years shows no abnormal physical effects. Dosage has been tapered over that period to a low but effective dose. Directions for research are discussed.

**Sexuality and Adolescents with Autism**
Rebecca Koller
*Sexuality and Disability* Volume 18, Number 2 June 2000 125 - 135
Department of Special Education, University of Utah, Salt Lake City, Utah

Abstract  Appropriate education in sexuality is critical to the development of a person's positive self-esteem. The development of a healthy self-image may overcome potential feelings of depression and loneliness for the person with autism. This paper addresses the need for and challenges to providing sexuality education to individuals with autism. It summarizes teaching methods and approaches which have proven to be successful with this population.

**Sex Matters in Autism and Other Developmental Disabilities**
Travis Thompson, et al
University of Kansas Medical Center, USA tthompson.@kumc.edu

We have paid little attention to gender differences in developmental disabilities aside from the purpose of establishing prevalence. Yet, studying sex differences in the incidence and presentation of developmental disability and mental health disorders may contribute to our understanding of the neural circuitry and neurochemistry of both the normal and the abnormal brain. Furthermore, investigation into gender difference may have practical implications, as we may need to design sex-specific interventions for persons with developmental disability. In this article, we first review sex differences in typically developing children as well as some of the literature on the biology proposed to explain those differences. We then explore differences in prevalence and presentation of several developmental and mental health disorders as they may relate to biological mechanisms–with special attention to autism. Finally, we look at research needs as they relate to sex in developmental disability.
High-functioning autism and sexuality: A parental perspective
Mark A. Stokes Deakin University, Australia, stokes@deakin.edu.au
Archana Kaur
Deakin University, Australia

Few studies have compared sexual behaviours among adolescents with high-functioning autism (HFA) and typical populations, and indicated whether specialized education is required. We hypothesized that adolescents with HFA would (1) display poorer social behaviours; (2) engage in fewer behaviours related to privacy and have poorer knowledge regarding privacy issues; (3) have less sex education; and (4) display more inappropriate sexual behaviours; and that (5) parental concerns would be greater for the HFA sample. Parents of typical adolescents ($n = 50$) and adolescents with HFA ($n = 23$) were surveyed with a Sexual Behaviour Scale (SBS) developed by the authors, with domains corresponding to the hypotheses. The HFA and typical groups were found to be significantly different on all five domains. However, following covariation with age and level of social behaviour, it was found that only parental concerns about their child distinguished between typical adolescents and those with HFA. Specialized sex education programmes with a social interaction emphasis should be considered for this group.

Course of Behavioral Change in Autism: A Retrospective Study of High-IQ Adolescents and Adults.
Piven, Joseph MD; Harper, Jennifer BA; Palmer, Pat PhD; Arndt, Stephan PhD

Abstract:
Objective: The course of behavioral change in autistic behaviors has received little attention in previous research but is a potentially important parameter for study in autism.

Method: Autistic behaviors were systematically examined in 38 high-IQ adolescent and adult autistic individuals at their current age (13 through 28 years) and retrospectively at age 5 years using a standardized interview for autism.

Results: Significant change over time in autistic behaviors, generally in the direction of improvement, was detected. The proportion of subjects showing improvement in communication and social behaviors was found to be significantly higher than the proportion showing improvement in ritualistic/repetitive behaviors. Five of 38 subjects who met DSM-IV criteria for autistic disorder at age 5 years no longer met criteria at their current age, although all five continued to have substantial impairment.

Conclusions: The study of patterns of behavioral change over time in autism has practical implications for both diagnosis and prognosis as well as potential importance in defining biologically meaningful subgroups and clarifying fundamental mechanisms underlying this disorder.

Peripheral markers of serotonergic and noradrenergic function in post-pubertal, caucasian males with autistic disorder.


University Center of Child and Adolescent Psychiatry, A.Z.M., Antwerp, Belgium.

Some studies have suggested that disorders in the peripheral and central metabolism of serotonin (5-HT) and noradrenaline may play a role in the pathophysiology of autistic disorder. This study examines serotonergic and
noradrenergic markers in a study group of 13 male, post-pubertal, caucasian autistic patients (age 12-18 y; I.Q. > 55) and 13 matched volunteers. [3H]-paroxetine binding Kd values were significantly higher in patients with autism than in healthy volunteers. Plasma concentrations of tryptophan, the precursor of 5-HT, were significantly lower in autistic patients than in healthy volunteers. There were no significant differences between autistic and normal children in the serum concentrations of 5-HT, or the 24-hr urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), adrenaline, noradrenaline, and dopamine. There were no significant differences in [3H]-rauwolscine binding Bmax or Kd values, or in the serum concentrations of tyrosine, the precursor of noradrenaline, between both study groups. There were highly significant positive correlations between age and 24-hr urinary excretion of 5-HIAA and serum tryptophan. The results suggest that: 1) serotonergic disturbances, such as defects in the 5-HT transporter system and lowered plasma tryptophan, may play a role in the pathophysiology of autism; 2) autism is not associated with alterations in the noradrenergic system; and 3) the metabolism of serotonin in humans undergoes significant changes between the ages of 12 and 18 years.

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Effects of diagnosis, race, and puberty on platelet serotonin levels in autism and mental retardation.

Department of Psychiatry, Cornell University Medical College, New York, USA.

OBJECTIVE: To reevaluate platelet serotonin (5-HT) levels in autism, measuring and controlling for effects of race and puberty. The specificity of hyperserotonemia for autism versus cognitive impairment is also assessed.

METHOD: Platelet 5-HT levels were measured in 77 individuals, aged 2 through 37 years, with autistic disorder; 65 normal controls; and 22 mentally retarded or otherwise cognitively impaired (MR/CI) prepubertal children. Effects of diagnosis, race, and pubertal status were evaluated by analysis of variance in separate pre- and postpubertal groups. 5-HT levels were expressed as ng/mL blood and ng/microl platelet volume.

RESULTS: Among prepubertal children, significant effects of diagnosis (ng/mL; F2,109 = 5.9, p = .004) and
race (F2,109 = 14.7, p < .0005) were found. Autistic youngsters had significantly higher 5-HT concentrations than controls, although the elevation (25%) was less than typically reported; MR/CI children had levels very similar to those of controls. White children had significantly lower 5-HT levels than black or Latino youngsters, regardless of diagnosis. Diagnosis and race effects were nonsignificant in the postpubertal group. Postpubertal subjects had lower 5-HT concentrations than prepubertal subjects (ng/mL; F1,114 = 28.5, p < .0005).

CONCLUSIONS: The data underscore the importance of matching for race and pubertal status in neuropsychiatric research and suggest that the prevalence of hyperserotonemia in autistic individuals may have been overestimated because of a failure to control for both variables. Hyperserotonemia was not found in MR/CI youngsters without autistic features.

Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,1,2 Caterina Nascimbene, MD,1,3 Chitra Krishnan, MHS1 Andrew W. Zimmerman, MD,1,4 and Carlos A. Pardo, MD1,2,5

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)-1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate immune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Ann Neurol 2005;57:000–000
Is there brain inflammation in autism?

Diana L. Vargas, MD
Biomedical Care

- Comprehensive plan for biological restoration.
- Dietary intervention
- Nutritional Support
• Melatonin
• Serotonin pathway – 5HTP - Tryptophan
• Methylation and Sulfation Chemistry
• Immunological treatments
• Heavy Metal Detox – generally via oral route
• Reduction of Medication Side-effects

Hyperbaric Therapy
HBOT Clinical Study – ASD Type Presentation
Gunnar Heuser MD, PhD
In any situation in which application of appropriate measurements gives concrete evidence of changes induced by treatment, the significance of limited numbers of patients is increased. In a sense, this FAS patient acted as his own control, which was facilitated by the level of documentation that the computer-generated neurocognitive evaluation was able to provide. **Low-pressure HBOT is a therapy with an extremely low risk profile and relatively low cost, with potential benefits that seem to be significant and measurable for a condition considered incurable, with no treatment at our disposal.** In this case, a youth with 15-year-matured FAS benefited from a short course of low-pressure HBOT and sustained durable cognitive improvements. Given the implications, these results should receive consideration for broader study as soon as possible.

**ASD Ring of Fire**
NON-Autism, but Sibling w/ADD and Anxiety – Mood Disorder Pattern
Mother of ASD Child Showing Post Traumatic Stress Disorder Pattern
## Starting - Out Prioritize

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<th>Treatment</th>
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<th>Got Better</th>
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<td>29%</td>
<td>30%</td>
<td>41%</td>
<td>1.4:1</td>
<td>283</td>
</tr>
<tr>
<td>Prozac</td>
<td>31%</td>
<td>32%</td>
<td>36%</td>
<td>1.2:1</td>
<td>1123</td>
</tr>
</tbody>
</table>