A Double-Blind Placebo-Controlled Trial of Fluoxetine for Repetitive Behaviors and Global Severity in Adults with Autism Spectrum Disorders

BACKGROUND:
- Advances have been made in Autism Spectrum Disorder (ASD) intervention research, but the majority of studies have been conducted in the pediatric population
- Autism Spectrum Disorders in adulthood are characterized by persistent functional deficits in core and associated symptom domains
- The growing needs of adults with ASDs are reflected in a 48% increase in prescriptions of psychopharmacological agents from 1993 to 2001
- Selective serotonin reuptake inhibitors (SSRIs) were the fastest growing class of psychopharmacological agents prescribed from 1993 through 2001

OBJECTIVE:
- To study the effects of fluoxetine and placebo on repetitive behaviors and global severity in adults with Autism Spectrum Disorders

METHODS:
- **Design**
  - Double-blind, randomized, parallel, controlled experimental; Duration: 12 weeks
- **Inclusion/exclusion criteria**
  - Inclusion: Age 18-60 years old, met DSM-IV criteria for an ASD, global severity ratings in the moderate or greater range (CGI score of 4 or higher) and medication free status
  - Exclusion: History of hypersensitivity or side effects while taking fluoxetine, abnormal ECG, laboratory test, or physical examination findings, subjects with schizophrenia, schizoaffective disorder, bipolar disorder, active seizure disorder, or significant hematopoietic or cardiovascular disease
- **Outcome measures**
  - Outcome measures: The compulsion subscale of the Yale-Brown Obsessive Compulsive Scale, Clinical Global Impression (CGI) improvement ratings, global rating, irritability subscale of the Aberrant Behavior Checklist, and the Hamilton Depression Rating Scale
- Number of patients enrolled
  - 22 patients were randomly assigned to fluoxetine and 15 were randomly assigned to placebo
- Drug regimens/dosages used
  - Study medications were dispensed in an identical double-blind fashion with a fixed schedule for the first week, starting with one 10 mg capsule in the morning after breakfast to minimize GI side effects and insomnia. In the 2nd week the dose was increased by 10 mg. In subsequent weeks it was increased by 20 mg per week as tolerated by the patient up to a maximum dose of 80 mg/day.
- Power
  - Power was not reported in the study
- Data handling method used
  - Intent-to-treat

RESULTS:
- 13 patients in the placebo group and 21 patients in the fluoxetine group completed the study
- **Outcome Measures**
  - The treatment-by-time interaction indicated a statistically significant greater reduction in the compulsion score in the fluoxetine group than in the placebo group (p=0.005)

- o There was also a statistically significant difference between fluoxetine and placebo in improvement on the global measure as rated by the treating clinicians (p=0.03)
  - o For the CGI measure of improvement in obsessive-compulsive symptoms, the clinicians' ratings demonstrated response rates of 50% for fluoxetine versus 8% for placebo. The chance of improvement was 1.8 times greater for fluoxetine as compared to placebo (p=0.03)
  - o In the ratings by independent evaluators, the difference between fluoxetine and placebo in improvement on the global measure was not statistically significant (p =0.07), nor was the improvement in obsessive-compulsive symptoms (p=0.25)
  - o The difference between fluoxetine and placebo on the weekly reduction in score on the irritability subscale of the Aberrant Behavior Checklist was also not statistically significant (p=0.15)
  - o The rates of suicidal ideation (defined as a score of 2 or higher on the HAM-D) were not statistically significant between treatment groups (p=1.00)
- Authors' Conclusion
  - o Fluoxetine treatment resulted in significantly greater improvement in repetitive behaviors, according to both the Yale-Brown compulsion subscale and CGI rating of obsessive-compulsive symptoms, as well as on the CGI overall improvement rating. Fluoxetine also appeared to be well tolerated.

STRENGTHS:
- Randomized placebo-controlled trial, double-blind

LIMITATIONS:
- Important weaknesses of the study include small sample size, possible inadequate alpha and power, likelihood of unblinding, subjective nature of the reporting of CGI, Yale-Brown Obsessive Compulsive Scale, and Aberrant Behavior checklist, duration of study, and broad inclusion criteria such as inclusion of all types of Autism Spectrum Disorders

CONCLUSION:
Further research is needed to determine the effectiveness of fluoxetine in Autism Spectrum Disorders. This study used the compulsion subscale of the Yale-Brown Obsessive Compulsive Scale to analyze improvements in repetitive behaviors. Future studies should track patients' chief complaints to allow for a better understanding of which behaviors are improving. Also, more appropriate outcome measures are needed such as the Social Responsiveness Scale which was developed to assess social deficits in ASDs, specifically. Further studies are also needed to determine if fluoxetine has a more favorable effect in individuals with a higher baseline compulsion level. In order to extrapolate the results appropriately, studies should focus on one aspect of the ASDs (such as Asperger's disorder only), because there can be significant variability between these disorders. Additional studies should be completed to compare different SSRIs, with larger sample sizes, adequate power and alpha, and of longer duration.

Reference: Hollander, E., Soorya, L., Chaplin, W., Anagnostou, E., Taylor, B., Ferretti, C., et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult Autism Spectrum Disorders. Am J Psychiatry. 2012; 169:292-299.

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