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Commentary on 'Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD)'

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This is a commentary on a Cochrane review, published in this issue of EBCH, first published as: Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews, 2010 Aug 4 (8):CD004677. Further information for this Cochrane review is available in this issue of EBCH in the accompanying Summary article.

Autism Spectrum Disorders (ASDs) are characterized by core symptoms of social deficits, communication abnormalities, and stereotyped/repetitive behaviors. Although a number of educational interventions, behavioral therapies and medications are commonly used in an attempt to reduce problematic symptoms and behaviors in children, adolescents, and adults with ASDs, none of these treatments are curative and many of the commonly used treatments have not been adequately studied to determine their efficacy. In clinical practice, psychotropic medications such as stimulants, neuroleptics, and antidepressants are sometimes used in an attempt to reduce either core ASD symptoms (such as stereotyped behavior) or co-existing symptoms such as inattention, hyperactivity, or agitation. The repetitive and stereotyped behaviors of ASD have some similarity to compulsive behaviors seen in obsessive-compulsive disorder (OCD), and this rationale has been used to justify treatment of such behaviors with SSRIs, which have established efficacy in the treatment of obsessive compulsive disorder (1, 2). In addition to treating the ASD core symptom of repetitive/stereotyped behavior, SSRIs may also be used as a treatment for co-occurring disorders such as depression or anxiety.

The prescription of SSRIs for individuals with ASDs is a common practice and may be increasing over time. According to a 1988-2005 longitudinal study of medication use in 286 adolescents and adults with ASD followed over a 4.5 year period, 57% were taking psychotropic medication at the beginning of the study and 64% were taking psychotropic medication at the end of the study (3). There was a statistically significant increase in the proportion taking psychotropic medications over time, and at both time points, the proportion taking psychotropic medication was higher for older individuals. SSRIs were among the most commonly prescribed medications, and the proportion taking this class of medication increased from 24% to 36% over the course of the study. Polypharmacy also increased over the course of the study, such that individuals took an average of 1.0 psychotropic medication at the start of the study and 1.4 medications at the study's end. In addition to this study (which involved samples from Massachusetts and Wisconsin), statewide surveys in North Carolina and Ohio also demonstrated frequent use of SSRIs in

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the treatment of ASD (4). An increase in the prescribing of psychotropic medications for individuals with ASD over the period of 1993 to 2001 in North Carolina was also noted.

The Cochrane review provides some support for the use of SSRIs in adults with ASD. The authors note that in this group, various SSRIs have shown efficacy in the treatment of obsessive-compulsive behaviors (fluvoxamine), anxiety (fluoxetine) and/or aggression (fluvoxamine) and have led to improvement in clinical global impression (fluoxetine and fluvoxamine). On the other hand, the review authors conclude that there is no evidence to support the use of SSRIs in children and adolescents with ASD, either for treatment of core symptoms or treatment of co-occurring non-core symptoms and behaviors. Also, they point out that SSRIs have a significant risk of causing harm, since side effects were sometimes more common in children treated with SSRIs than in children assigned to placebo. While we agree with many of the reviewers' findings, we would posit that the summary statement that there is no evidence of SSRI efficacy in children with ASD is based on an extremely limited and inadequate number of studies and target symptoms. We are also concerned that the positive outcomes of the Hollander et al. (2005) study may not have received adequate attention (5). Although this was a small study which used complex methods to evaluate multiple outcome measures (some of which showed no treatment effects), the study results provided some evidence of fluoxetine's efficacy in treating repetitive behaviors in ASD, and the low-dose liquid formulation was reasonably well tolerated. We list some specific concerns about existing studies of SSRI treatment for ASDs below:

Sample Heterogeneity

It is possible that benefits from SSRI treatment in young people with ASD were undetectable because of heterogeneity of treatment response among individuals with ASDs. As mentioned in the Cochrane review, large trials are needed to investigate any subgroup differences in medication responses. The authors of the review mention pre- vs. post-puberty and low vs. high IQ as relevant comparisons. We also suggest that other variables, such as high vs. low overall ASD core symptom or target symptom severity may be relevant. For example, it is possible that patients with more severe forms of ASD (for example non-verbal individuals with autistic disorder and high levels of agitation) will be less responsive to SSRI treatment and may also be more susceptible to side effects from SSRIs. Higher functioning individuals with diagnoses of Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) may show better responses to SSRIs. Also, changes in the severity of some target symptoms (such as repetitive behavior) may be undetectable in individuals with very low baseline rates of that target symptom.

One possible reason for failure to find improvement in global impression scores could be the presence of behavioral side effects in a subset of study subjects. Even if some of the target behaviors improved, the presence of such side effects could lead to an overall worsening of behavior in some individuals, and this could affect ratings of overall global improvement. A commonly described side effect of SSRIs in children is a behavioral activation or disinhibition syndrome (1, 6, 7). Behavioral side effects in the activation/disinhibition category may be particularly common in children with ASD after initiation of treatment with an SSRI (1). It is unclear to what extent this category of side effects in a subset of study subjects may have obscured the detection of any positive effects of SSRIs in children with ASD, but some of the side effects reported in the reviewed studies are consistent with activation/disinhibition. Detailed measures of behavioral side effects will be important in future studies of SSRIs in ASD. If it is determined that specific SSRIs are less likely to cause behavioral activation side effects, such drugs might be preferred over other SSRIs in the treatment of ASD. As suggested by one of the studies referred to in the review (8), treatment response may also be associated with specific genetic polymorphisms. It is possible that genetic polymorphisms will be found to be associated with target symptom

improvement as well as susceptibility to behavioral activation and other side effects from a drug. Pharmacogenetic studies may eventually lead to individualized drug selection based on a patient's genetic profile.

Target Symptoms and Assessment Tools

Improved definition of target symptoms and inclusion criteria requiring a threshold level of baseline target symptom severity may be helpful in future studies. If stereotyped/repetitive behavior is the target symptom, it would be reasonable to require that this particular symptom domain lead to behavioral disruption that interferes with school and/or home life. There may be a ceiling effect for individuals who have only mild symptoms at baseline and would be unable to improve to a degree that is clinically and statistically significant. Outcome measures in studies of SSRIs in ASD have included interviews with clinician ratings of global improvement (CGI) and/or questionnaire-based instruments that inquire about repetitive behaviors typical of ASD and/or obsessive-compulsive disorder. In some cases, the CGI may be too broad of a measure, especially if it includes consideration of all problematic symptoms and behaviors rather than specific target symptoms. For example, it seems unlikely that a CGI that includes consideration of overall ASD severity would be significantly impacted by a change in the frequency or severity of a child's repetitive behaviors. Instead, more specific questions measuring the frequency of repetitive behaviors, severity of distress during transitions or forced interruption of repetitive behavior, disruptive behavior in response to changes in usual routines, and degree to which teachers/parents/others have to modify the child's environment or adjust their own plans to accommodate the repetitive/stereotyped behaviors may be useful. Observational assessments that are able to quantify frequency of stereotyped/repetitive motor behaviors may also be helpful. Investigators may also want to obtain specific examples of repetitive behaviors from the caregivers of individual study subjects and ask caregivers to rate the frequency, severity, and impairment from these specific target symptoms throughout the course of the medication trial. Ratings of the impact of such behaviors on family life could also be used. Considering the studies discussed in the Cochrane Review, one instrument that comes close to measuring individualized target behaviors in this manner is the CY-BOCS-PDD, which includes questions regarding specific OCD-like compulsive behaviors and repetitive behaviors typical of ASD, followed by scales that rate the severity of time spent, interference, distress, resistance, and control with reference to the behaviors reported to be present (9). However, even this instrument may not be sensitive enough to detect some types of clinically significant behavioral improvements. While tools such as the CY-BOCS-PDD are available to measure repetitive behaviors, the field has few options for adequately measuring target symptoms of anxiety or depression (especially in individuals with more limited language skills). The authors of the Cochrane review suggest that, on a case-by-case basis, it is reasonable to use SSRIs in children with ASD when targeting symptoms of co-occurring disorders for which the drugs are approved. However, it is not clear whether SSRIs have the same efficacy for such disorders when used in individuals with ASD. In future studies, it would be helpful to include anxiety and depression as target symptoms. Since symptoms of these disorders may present differently in ASD than non-ASD subjects, it may also be important to develop improved measures of anxiety and depression designed specifically for use in individuals with ASD.

Other SSRIs

The authors of the review note that no adequate randomized controlled trials of paroxetine, sertraline, or escitalopram have been conducted. It is possible that these agents may be more effective or associated with fewer side effects than the SSRIs used in existing randomized controlled trials. Sertraline may be particularly appropriate for study since it already has an FDA indication for pediatric OCD. One of us (AR) suspects based on clinical experience

that paroxetine is somewhat less likely than other SSRIs to cause a disinhibition syndrome. This hypothesis is based on observations of multiple young clinic patients with ASD who developed behavioral disinhibition on a first and/or second SSRI trial but subsequently benefitted from low-dose paroxetine without the occurrence of disinhibition side effects that were observed with previous SSRIs. Although the half-life of paroxetine is relatively short and this characteristic may increase the likelihood of discontinuation effects when doses are missed or prior to the next scheduled dose, the short half life may be advantageous if the drug must be discontinued due to behavioral disinhibition (behavioral side effects should wear off faster after discontinuation or reduction in dose if a drug with a short half life is used). Disadvantages of paroxetine include the lack of currently approved pediatric indications and its interference with the metabolism of multiple other drugs. However, if paroxetine turned out to be efficacious and better tolerated than other SSRIs, the risk/benefit ratio of its use in ASD might be favorable.

Combination Therapy

Medication trials focusing on combination therapy are greatly needed. Although polypharmacy in the treatment of individuals with ASD seems to be an increasingly common occurrence (3), clinical trials using combination treatments are not available to inform us regarding the safety and efficacy of prescribing multiple psychotropic medications at once. Randomized controlled trials comparing single agents to placebo and a combination of two drugs would be helpful. For example, a study comparing treatment responses for individuals treated with an SSRI alone vs. SSRI plus a stimulant (or SSRI plus a neuroleptic) vs. placebo could be done. Appropriate target symptoms for each drug as well as measures of overall functioning would be appropriate outcome measures.

Summary

The Cochrane review clearly provides important guidance for current clinical practice. There is a reasonable amount of support for the use of SSRIs to treat repetitive behaviors (and perhaps other core symptoms) in adults with ASD. Since review of existing studies does not support the efficacy of SSRIs in children and adolescents with ASDs, any use of these drugs within this younger age range should be done cautiously. We recognize that few psychotropic medications are specifically approved for use in children with ASD, and providers may choose to treat such patients in an off-label manner based on mechanistic hypotheses about possible beneficial drug effects or the presence of symptoms similar to those of other disorders for which SSRIs are approved. If clinicians offer to prescribe SSRIs to children with ASD, it is important that they inform parents about the lack of evidence of their efficacy in RCTs, discuss the potential risks (including behavioral side effects), and discuss alternative pharmacological and non-pharmacological treatments. When treating individuals in an off-label manner, it is particularly important to define clear target symptoms and assess whether such symptoms have improved with addition of the drug, keeping in mind the possibility of placebo effects and adverse drug reactions. If a drug does not seem to produce significant benefit or if side effects outweigh any beneficial effects, it is important to discontinue the ineffective drug rather than continuing that drug while adding on new medications. Given the evidence of adverse behavioral side effects from SSRIs in young patients with ASD, caution should be used with initial dosing and side effects must be closely monitored. The use of low initial doses and slow upward titration may help to reduce side effects. As a general rule, one of us has previously suggested starting with a half tablet of the smallest available tablet size and increasing by a half tablet per week to reach a moderate target dose (1). For example, in the case of sertraline, the recommended starting dose for treatment of obsessive-compulsive disorder in children age 6-12 years is 25mg (smallest tablet size), so starting at half that dose (12.5 mg) would be reasonable when

treating a child in this age range who may be at some increased risk of behavioral side effects due to an ASD diagnosis. The dose could then be increased by 12.5mg per week (if well tolerated) to an initial target dose of 25-50 mg and held at 25-50mg for 4-6 weeks before any further increase is considered. Liquid formulations can allow for even smaller starting doses in children at the lower end of this age range or in those who have shown sensitivity to side effects of other medications. For adolescents and adults with ASD, it may also be advisable to start a bit below the FDA-recommended starting dose for the drug and to use a relatively slow upward titration. If side effects occur during upward titration, these may decrease with a dose reduction. If disinhibition is severe and present even at low doses, or if the medication does not result in symptom improvement, the SSRI should be tapered off and discontinued. Finally, we agree with the Cochrane review's call for additional study of SSRIs in ASD, including examination of possible sub-group variables, larger trials, examination of other target symptoms in children with ASD (e.g., anxiety, depression) and RCTs with three yet unstudied SSRIs.

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