Venlafaxine has modest effects in autistic children

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Objectives: Few controlled psychopharmacologic trials have been conducted in autistic children to determine which agents may be effective at alleviating associated symptoms. **Methods:** Fourteen male children (7.1 ± 3.0 years) with autistic disorder, diagnosed by ICD-10 criteria, completed a placebo-controlled, double-blind crossover trial of venlafaxine (Effexord®, Wyeth) administered at a dosage of 30 mg daily for 6 weeks. Subjects were included in the study if their eye contact and expressive language were inadequate for their developmental level. Subjects had not tolerated or responded to other psychopharmacologic treatments (neuroleptics, methylphenidate, clonidine or desipramine). **Results:** Teacher ratings on the Aberrant Behavior Checklist irritability, stereotype and inappropriate speech factors were lower during treatment with venlafaxine than during treatment with placebo. Clinician ratings (Children's Psychiatric Rating Scale Autism, Anger and Speech Deviance factors; Children's Global Assessment Scale; Clinical Global Impressions Efficacy) of videotaped sessions were not significantly different between venlafaxine and placebo. **Discussion:** Venlafaxine was modestly effective in the short-term treatment of irritability in some children with autistic disorder.

Keywords:
autistic disorder, neuroleptics, venlafaxine

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Autistic disorder is a chronic pervasive developmental disorder, characterized by qualitative impairments in reciprocal social interaction, verbal and nonverbal communication and imaginative activity with a markedly restricted repertoire of activities and interests. Additionally, hyperactivity, poor attention span and impulsivity are often prominent associated clinical features and have been target symptoms in previous trials [1]. In an earlier open trial of dextroamphetamine, autistic children had an adverse response [2]. Jaselskis and colleagues [3] and Hunt and coworkers [4] report good efficacy of clonidine treatment of autistic children. An open trial suggested that methylphenidate use in autistic hyperactive children may ameliorate hyperactivity, inattention and impulsivity in children with autistic disorder [5]. Neuroleptics are somewhat effective in reducing hyperactivity, impulsivity and inattention in children with autistic disorder [6]. However, chronic use of neuroleptics may be complicated by cognitive blunting and the often irreversible side effect of tardive dyskinesia [7]. The development of efficacious and safe therapeutic interventions remains an area of significant need in this disorder. Therapeutic effects in other disorders with similar target symptoms may guide development of treatments for children with autistic disorder.

We found only one study investigating the efficacy of venlafaxine (Effexord®, Wyeth) treating children suffering from autism [8]. These authors report only a modest improvement of symptomatology after administration of venlafaxine. Venlafaxine affects the serotonin system and has a relatively short half-life.

For that reason, this placebo-controlled study was conducted to examine the effects of venlafaxine on a variety of target behaviors in young boys with autistic disorder.

Methods

Fourteen outpatient male children (age range 5.2–11.7 years; mean = 7.1 years; SD = 3.0 years) meeting ICD-10 criteria for autistic disorder were recruited from the community and clinic. Full-scale intelligence quotas (IQs) ranged from 55 to 79 (67 ± 12) and were obtained from several tests, including the Wechsler Intelligence Scale for Children Revised, Leiter International Performance Scale, or the Cattell Infant Intelligence Scale. A 15th subject entered the study but was excluded due to noncompliance with medication and rating scales during the first week of the study. Agreement of the independent diagnosis of autistic disorder by at least two child and adolescent psychiatrists was obtained. The developmental and language levels of all subjects were assessed. Parents provided written

informed consent for their children after the procedures and possible side effects were explained to them. Assent was obtained from the two children who appeared to be capable of expressing it.

The subjects had no history of identified medical or neurologic illnesses and had been off medications for at least 1 month before the study. All of these children had been treated with either methylphenidate, neuroleptics, or desipramine before entry into the study. In each case, these medications had either been ineffective or caused intolerable side effects.

All subjects lived at home with either both parents (12 subjects) or their mothers (two subjects). Socioeconomic status for the subjects' families was class I (five subjects), class II (five subjects) and class IV (four subjects) [9]. Two childrens' languages consisted of monosyllabic utterances, another two consisted of single words (10-word vocabulary) and the other children spoke in sentences. However, all children had social and pragmatic language deficits consistent with autistic disorder.

All raters (teachers and clinicians) were blind to drug order until ratings were completed.

Teacher-rated instruments included weekly ratings. Side effects monitored included increased thirst, drowsiness, sleep disturbance, sadness, dizziness, irritability, appetite change and decreased activity. Parents and teachers responded with 'yes' (coded as 0) or 'no' (coded as 1) for each item each week. These Symptom Checklist responses were summed over each 6-week treatment period. Weekly teacher ratings included the Aberrant Behavior Checklist (ABC) [10].

A 15-minute videotape paradigm was constructed to determine clinician ratings of the effects of venlafaxine on inadaequate eye contact and expressive language deficits. There were three sessions that were performed at baseline and at the end of each treatment period. The videotaping was carried out in a small office with the equipment visible in the room. The first 5 minutes of taping were free play. The second 5 minutes consisted of tasks with the parent, including: copying a square and a circle and drawing a picture; the parent asking the child to name an object; verbalizing the name of a 'Cup'; standing in front of the mother while she straightened the child's clothes; and having the parent leave the room and return after a few minutes. The last 5 minutes consisted of parent reunion, asking for assistance with clean-up and leaving the room with the child. Clinician ratings (average of both raters) consisted of videotaped observations at baseline, 6 weeks and 13 weeks using the Children's Global Assessment Scale [11], modified Children's Psychiatric Rating Scale (CPRS) [12] and Clinical Global Impressions [13].

This was a double-blind and placbo-controlled crossover study. Venlafaxine and identical placebo tablets were administered for 4 weeks (dosage: 30 mg daily). The subjects were randomly assigned by a nonrating clinican to begin venlafaxine or placebo. Patients were free of medication for at least 4 weeks (12 weeks for a single subject who bad been taking fenfluramine [Pondim®, American Home Products]) before beginning the study but there was no placebo washout phase. Blood pressure and clinical symptoms were monitored via telephone conversations and scheduled visits. School nurses or the family physician measured blood pressure on a weekly basis.

Subjects continued to receive educational and behavioral interventions in school during the course of the study that were not substantially altered for any of the children during their participation in the study.

Parent and teacher ratings and clinician ratings were made at the end of the treatment period. Ratings during placebo and drug treatment were compared using paired, two-tailed t-tests. Statistics were computed using SPSS V9.0.

Results

Teacher's ratings on the ABC factors: irritability (placebo: 15.1 ± 4.9; venlafaxine: 12.6 ± 7.4; $p = 0.042$); hyperactivity (placebo: 23.2 ± 12.1; venlafaxine: 20.4 ± 11.5; $p = 0.035$); inadaequate eye contact (placebo: 8.4 ± 5.2; venlafaxine: 7.0 ± 3.4; $p = 0.042$) and lethargy (placebo 6.8 ± 2.5; venlafaxine: 5.1 ± 3.2; $p = 0.043$) were significantly improved on venlafaxine. The scores revealed a significant increase in drowsiness (placebo: 1.6 ± 0.4; venlafaxine: 3.8 ± 2.8; $p = 0.024$) and decreased activity (placebo: 3.2 ± 2.5; venlafaxine: 4.6 ± 2.9; $p = 0.032$). None of the clinician ratings showed significant differences between placebo and venlafaxine.

None of the subjects appeared to have hypotonia, headaches or stomach aches, although report of such side effects was limited by the expressive language and social skills of these subjects.

Discussion

This double-blind, placebo-controlled study examined the effects of venlafaxine in male autistic children between the ages of 5 and 11

Highlights

- There is currently no 'gold standard' treatment with respect to the psychopharmacological treatment of autistic disorders.
- Clonidine, methylphenidate are reported as to be only modestly effective.
- Neuroleptics are the most effective therapy, but their long-term use leads to severe adverse side effects.
- Selective serotonin re-uptake inhibitors such as venlafaxine show almost no side effects, but are only modestly effective in the treatment of autistic disorders.

with inadequate eye contact and expressive language deficits. Teacher and parent ratings showed a modest symptom improvement while the child was taking venlafaxine. Teachers rated significant behavioral changes while the boy was on venlafaxine. Clinician rating scales were insensitive to venlafaxine effects. Although inadequate eye contact and expressive language deficits were the primary target symptoms of this study, the treatment effect of greatest size was a 33% decrease of symptomatology. Interestingly, in a recent trial of clomipramine in autistic disorder, an improvement in the anger scale of the CPRS was the strong but unexpected effect [14].

There are very few specific clinical instruments that target the response of inadequate eye contact and expressive language deficits to drug treatment in autistic persons. Both parents and teachers remarked that several of the items of the questionnaire were irrelevant for evaluating their autistic child.

The failure of the clinician ratings to be sensitive to changes may have been influenced by several factors. Although clinician-rated effects at 1 month were equivalent to ratings at 2 months in a study of venlafaxine treatment of nonautistic children with attention deficit disorder and hyperactivity [4], 6 weeks may have been an inadequate duration to determine full venlafaxine effect in the current study. The environment in which clinician ratings were performed was not optimal to serve as a sensitive indicator of the modest effects of venlafaxine during the 6-week trial. The videotape equipment was a focus of curiosity and attention. Several of the subjects associated their visits with blood draws done after the videotaping. Some of the children verbalized their anxiety about the blood-drawing procedure during the taping sessions. In addition, the videotaping was done in a small office, which may have limited the subjects' movement. This highly structured and defined space was not the same as that in which the teachers and parents observed the children. It would have been preferable to make clinician ratings in each child's home and school setting. Since this may he impractical for most out-patient clinicians, ratings by teachers and parents arc invaluable in the assessment of children with autistic disorder during psychopharmacologic treatment. Possible 'unblinding' of parents and teachers because of side effects is another limitation of the study. Videotapes were rated by the clinicians several months after each patient's treatment period ended and clinicians were unable to make accurate assessments of which drug phase during review of the videotapes. Another methodologic issue of concern was possible carryover, which was minimized by a 1-week taper during the crossover period. In addition, a small number of subjects was involved in this study.

Finally, other antidepressants did not show sufficient efficacy in our patients. Although our results are comparable to those of trials with other depressants, this bias may have influenced our findings.

Clinical implications

Eight of the 12 subjects were treated with Venlafaxine in an open manner after the study. All of these eight subjects continued to respond with a symptom improvement within 6 weeks.

Venlafaxine's modest effects in the treatment of a subgroup of children with autistic disorder may be related to noradrenergic dysregulation as indicated by findings, such as increased plasma noradrenaline in children with autistic disorder [15,16].

Limitations

Although this study revealed a modest therapeutic effect of venlafaxine in the acute management of autistic children, in some subjects it is clear that its role in the management of these symptoms in children with autistic disorder may be limited. Venlafaxine's role in acute and chronic treatment of these symptoms requires further investigation. Controlled, chronic pharmacologic trials with clinical observations in the school and home settings will be necessary to delineate further the role of venlafaxine in treating this specific population.

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