

Olanzapine in the Treatment of Developmental Stuttering: A Double-Blind, Placebo-Controlled Trial

GERALD A. MAGUIRE, M.D., GLYNDON D. RILEY, Ph.D., DAVID L. FRANKLIN, MHA, Psy.D., MICHAEL E. MAGUIRE, MA, Psy.D., CHARLES T. NGUYEN, M.D., and PEDRAM H. BROJENI, B.S.,

Department of Psychiatry, University of California, Irvine, California, USA

Stuttering is a speech disorder that affects one-percent of all adults and much has been learned recently of its neurologic correlates. Stuttering has been associated with excessive cerebral activity of the neurotransmitter, dopamine. Pharmacologic research has suggested that older generation dopamine antagonist (i.e. “typical antipsychotic”) medications improve stuttering symptoms, but are associated with poorly tolerated adverse effects. The purpose of this study was to compare the efficacy and tolerability of olanzapine, a novel dopamine antagonist (or “atypical antipsychotic”), versus placebo in the treatment of adult developmental stuttering. Twenty-four adults who stutter participated in a twelve-week, randomized, double-blind, placebo-controlled trial conducted at two separate sites. Subjects received either olanzapine (2.5 mg titrated to 5 mg) or matching placebo. Subjects were rated on an objective measure of stuttering severity (SSI-3), a clinician based global impression (CGI), and a subject-rated self-assessment of stuttering (SSS). Subjects were also monitored for potential side-effects. Twenty-three of the twenty-four subjects enrolled in the trial successfully completed the full course of the study. Olanzapine was statistically superior to placebo on the three ratings of stuttering severity, the SSI-3, the CGI and SSS ($p < .05$). Olanzapine is a promising medication for the treatment of stuttering and further research is warranted.

Keywords Stuttering; Medication; Olanzapine; Dopamine.

INTRODUCTION

Stuttering is a speech disorder characterized by frequent prolongations, repetitions or blocks of spoken sounds or syllables. Stuttering is a common disorder affecting four

Michael E. Maguire is also on the faculty of Sierra Cascade Research Associates, Paradise, California, USA.

Funded in part by a private research grant by R.G. Kirkup (Account Number: 455465-56620) and a research grant from Eli-Lilly and Company (Account Number: 485465-59441).

The authors would like to express their appreciation to the following individuals for their assistance and guidance in conducting the research study: Gerald E. Maguire, M.D., Tony Ortiz, B.S., Thomas M. Johnson, M.D., Lawrence Plon, Pharm.D., and Louis A. Gottschalk, M.D., Ph.D.

Address correspondence to Gerald A. Maguire, M.D., Department of Psychiatry, University of California, Irvine, UCIMC, 101 City Drive, Orange, CA 92868. E-mail: gamaguir@uci.edu

percent of children and one percent of adults and is classified in DSM-IV as an Axis I illness and by definition, interferes with social, academic or occupational functioning (1). Individuals who stutter often develop avoidance behaviors or social anxiety related to the speech dysfluency (1–3). Although cases of “acquired” stuttering with onset in adulthood exist, they are rare and are secondary to a known cause such as medications, or cerebral insult (4). Stuttering is primarily a developmental disorder with the onset of symptoms usually by the age of six years with many cases persisting into adolescence and adulthood (1–5). Speech therapy is most effective in children under the age of six years, necessitating the need for novel treatments for adolescent and adult stuttering (6). Traditional, once a week, adult stuttering speech therapy usually takes two years or more to achieve clinically significant efficacy (7).

The understanding of stuttering has evolved tremendously in recent years. Originally thought to be a disorder of psychologic origin, more is now known of its genetic and neurologic aspects. Stuttering is present in a 3:1 male to

female ratio with pair-wise concordance for identical twins (63%) being greater than fraternal same-sex twins (19%) (8–9). Emerging evidence strongly suggests that stuttering is related to abnormalities in the basal ganglia with hyperactivity of the neurotransmitter dopamine (10–13).

Prior pharmacological research has suggested that dopamine-blocking medications such as haloperidol and thioridazine improve stuttering symptoms (14,15). However, these typical antipsychotic agents were associated with many side effects in this patient population and treatment compliance was very low (16). Risperidone, a novel dopamine antagonist (atypical antipsychotic), has been shown in a well-controlled study to improve stuttering symptoms. It too, however is associated with untoward adverse events most commonly related to prolactin elevation (e.g., sexual dysfunction and amenorrhea (3). Olanzapine is an additional atypical antipsychotic agent which demonstrates broad neurotransmitter effects including dopamine blockade, serotonin blockade, acetylcholine release and glutamate modulation (17,18). Olanzapine has a low potential for motor system side-effects such as Parkinsonism and tardive dyskinesia and has minimal effects on prolactin (19). Preliminary, open-label studies suggest olanzapine to be efficacious and well-tolerated in child and adolescent stuttering (20).

Although antipsychotic agents may exhibit sedating qualities, it is likely that their demonstrated efficacy in stuttering is related to their effects on dopamine and not to merely an anti-anxiety or sedating effect. Benzodiazepines and barbiturates, being anxiolytics and highly sedating, were found to have no beneficial effects over placebo in the treatment of stuttering (16).

Prior research suggests that excessive dopamine reduces the efficiency of speech and motor programming at the striatum (21,22). Dopamine blocking medications, such as olanzapine, may therefore improve the efficiency of the striatum resulting in decreased stuttering. The purpose of this study was to investigate the efficacy and tolerability of olanzapine compared to placebo in the treatment of adult developmental stuttering.

METHODS

Twenty-four adults who stutter (ages 18–55) by DSM-IV-TR criteria participated in a two-center, three-month, double-blind, placebo-controlled trial of olanzapine (dose range 2.5 mg titrated at four weeks to 5 mg). Subjects were excluded if they had substance abuse, a major neurologic condition, or a DSM-IV Axis I psychiatric disorder other than stuttering. All subjects received full and informed consent within the guidelines of the University of California, Irvine Institutional Review Board and the Western Institutional Review Board. As part of the informed consent

process, all subjects were educated as to the possibility of weight gain associated with olanzapine therapy. Three females and twenty males completed the study with a mean age of 33 years (range 18–56) and an average of fourteen years of education. One subject who received placebo was dropped from the study after randomization because of the onset of major depressive disorder. The ethnic background of this sample included eighteen patients who were Caucasian, two patients of Asian descent, and three patients who were Hispanic. All subjects had the onset of stuttering in childhood prior to 8 years of age and stuttering severity ranged from mild to severe as assessed by the Stuttering Severity Instrument (SSI-3) (23). Furthermore, four patients were left-handed and nineteen patients were right-handed.

The subjects were randomized in a 1:1 fashion to either olanzapine or placebo. Severity of stuttering was rated at two baseline visits and then at the end of twelve weeks of double-blind treatment. All subjects began at 2.5 mg/day of olanzapine or identical placebo for the first four weeks and then increased to 5.0 mg/day the last eight weeks.

Since the severity of stuttering can vary over time in individuals, subjects were rated twice over a four-week baseline rating period prior to randomization. Subjects were rated on an objective measure of stuttering severity (SSI-3), a clinician based global impression (CGI) and a subject-rated self-assessment of stuttering severity (SSS) (24). The SSI-3 was performed via analyzing an audio/videotape of each subject speaking 200–500 words of standardized conversation and reading tasks administered randomly. The SSI-3 incorporates ratings of the percent syllables stuttered of syllables spoken (%SS), the duration of stuttering events, and the physical concomitants of stuttering behavior such as associated struggle and tic motions. These measures are combined to provide an overall measure of stuttering severity (the SSI-3). Subjects were rated on the SSI-3 by two speech–language pathologists trained in the assessment. Baseline and week 12 on double-blind treatment were scored independently and inter-rater reliability averaged 87% on the individual ratings. The average of their scores was used to compute changes in each measure. By using the combined rating of both observers, the reliability was higher than 87%.

Subjects were also monitored for potential side effects. At monthly visits, subjects were assessed for dopamine-related neurologic side effects such as Parkinsonism, akathisia, and tardive dyskinesia using the Simpson-Angus Scale, Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (25–27). Potential physical side effects were assessed by a physical examination and review of systems at each visit. At baseline and at the conclusion of the study, all subjects had fasting blood glucose levels monitored as novel dopamine antagonists have been reported to be associated with hyperglycemia (28).

Changes in stuttering associated with olanzapine were compared with changes associated with placebo for the Stuttering Severity Instrument (SSI-3), the Clinical Global Impression (CGI), and the severity subtest of the Subjective Stuttering Scale (SSS). The data were analyzed using the student t-test for unrelated samples. A confidence level of .05 was selected to define statistical significance.

RESULTS

Olanzapine was found to be statistically superior to placebo on the three ratings, the SSI-3, the CGI and SSS. On average, stuttering severity improved 33% on olanzapine (*sd*, 29), and 14% on placebo (*sd*, 19) on the SSI-3. Olanzapine was statistically superior to placebo on the SSI-3 ($p = .044$, *df*, 20.8; t , 1.8) (Figure 1). The subjects on active medication showed an average change on the CGI of 3.0 (*sd*, .82) which represented moderate improvement. Those in the placebo group averaged 3.9 (*sd*, .38) which represented essentially no improvement. This difference was significant at $p = .034$ (*df*, 9.3; t , 2.52). The SSS revealed an improvement of 22% on olanzapine (*sd*, 25) and <1% on placebo. This difference was significant at $p = .018$ (*df*, 18.3; t , 2.6) (Figure 2).

No subject in either treatment group experienced dopamine-related neurologic side-effects such as Parkinsonism, akathisia, or tardive dyskinesia. The only notable side effects of active treatment were mild sedation and weight gain, with an average of 3.5 kg (range 0.5–9.5 kg; *sd*, 2.5) on olanzapine versus –.35 kg (range –9.1–4.5 kg; *sd*, 3.5) on placebo. The mean body mass increase observed on olanzapine was 4.5% (range .5–14.5%) and for placebo, –.3% (range –9.5–5.3%). The weight gain on olanzapine was statistically greater than placebo ($p = .007$, *df*, 21.8; t , 3.1). No subject developed an elevation of fasting blood glucose

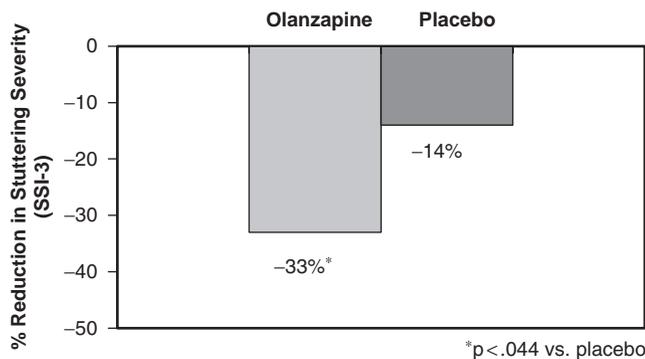


Figure 1 The SSI-3 is a reliable and valid objective measure to evaluate a subject’s fluency. Accordingly, this study found there to be on average a 33% reduction in dysfluency in the olanzapine group compared to an average change of 14% in the placebo group.

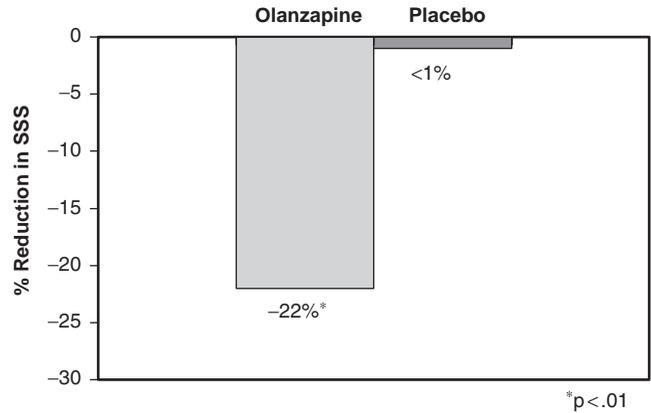


Figure 2 Percentage reduction in subject self-assessment of stuttering severity (SSS). The SSS is a self-administered, subjective scale of the subject’s stuttering. Four items related to severity are rated before and after the medication. The subjects on olanzapine improved 22% and those on the placebo improved less than 1%.

during the study. All subjects elected to take olanzapine voluntarily at the conclusion of the trial.

DISCUSSION

The effects of olanzapine in reducing stuttering symptoms (33% decrease) reveal perhaps a greater result than that seen with traditional speech therapy in a shorter period of time (7). Olanzapine may exert its therapeutic effect in stuttering at least in part through blockage of dopamine. Olanzapine is an atypical antipsychotic agent with effects on multiple neurotransmitters including dopamine, serotonin, histamine, acetylcholine and glutamate (16,17). Olanzapine’s effects on stuttering are likely not related to its effects on serotonin as Stager concluded that a selective serotonergic agent (e.g., paroxetine) had no effect (either positive or negative) on stuttering compared to a positive response with pimozide, a dopamine-blocking compound (29). Histamine blocking agents have not shown efficacy in stuttering in prior studies, suggesting that this activity is not related to olanzapine’s efficacy (30). Olanzapine does exert a positive effect on acetylcholine transmission (16). However, such cholinergic transmission is likely not related to its therapeutic effect given that bethanechol, a cholinergic compound, was found to not separate from placebo in a trial of stuttering (31). An area of intrigue is olanzapine’s effects on glutamatergic transmission. Olanzapine is unique from other dopamine blocking agents in modifying glutamatergic transmission (18). Early anecdotal reports suggest efficacy of glutamic acid in reducing stuttering severity (32,33). In a limited study, stuttering was found to be associated with abnormalities in the glutamatergic system (34). Further research is

warranted to investigate the possible role of glutamate in stuttering and whether the effects at this neurotransmitter system explain, at least in part, the efficacy of olanzapine.

In contrast to effects of other dopamine-blocking medications in stuttering, olanzapine was shown to be well-tolerated with high patient compliance (16,28,35). Limitations of the study include a modest sample size of 23 subjects and a limited duration of study (three months). Longer-term, multi-center studies with a larger sample size are necessary to further evaluate the efficacy and safety of olanzapine in adult developmental stuttering. Further research is also indicated to further elucidate the therapeutic mechanism of action of olanzapine in stuttering. Since stuttering is a developmental disorder and usually begins in childhood, studies of olanzapine in child and adolescent stuttering are indicated as well as studies investigating the combined results of olanzapine with speech therapy.

CONCLUSION

This study suggests that olanzapine is a useful, well-tolerated medication for the treatment of adult developmental stuttering.

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