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# Parent report of antidepressant, anxiolytic, and antipsychotic medication use in individuals with Williams syndrome: Effectiveness and adverse effects

Marilee A. Martens [a,b,*], Daisha L. Seyfer [c], Rebecca R. Andridge [d], Jessica E.A. Foster [e], Monali Chowdhury [a], Kelsey E. McClure [f], Daniel L. Coury [c]

[a] The Nisonger Center, The Ohio State University, Columbus, OH 43210, USA
[b] Department of Psychology, The Ohio State University at Newark, Newark, OH 43055, USA
[c] Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH 43205, USA
[d] Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH 43210, USA
[e] Bureau for Children with Medical Handicaps, Ohio Department of Health, Columbus, OH 43216, USA
[f] Department of Psychology, The Ohio State University, Columbus, OH 43210, USA

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ABSTRACT

Williams syndrome (WS) is a neurodevelopmental genetic disorder characterized in part by anxiety and behavioral difficulties. We examine the effectiveness and adverse effects of antidepressant, anxiolytic, and antipsychotic medications in individuals with WS. A total of 513 parents/caregivers completed a survey of psychotropic medication usage regarding their child or adult with WS. Twenty-four percent (24%) of the individuals had been prescribed an SSRI medication, while 12% had been prescribed another type of antidepressant or anxiolytic. Overall, 81% of respondents indicated that SSRI medications were either "Helpful" or "Somewhat Helpful", with paroxetine reported to be the least helpful. Sixty-four percent (64%) of survey participants reported that non-SSRI antidepressants and anxiolytics were either "Helpful" or "Somewhat Helpful" in treating symptoms of anxiety. Side effects for the antidepressants and anxiolytics were typically neurological in nature. Ten percent (10%) of the survey participants reported taking an antipsychotic medication, with risperidone and quetiapine described as more helpful than aripiprazole. Medication effectiveness may be related to the impact on serotonin levels. These findings call for further studies of medication usage in WS in order to improve their quality of life.



## 1. Introduction

Williams syndrome (WS) is a neurodevelopmental genetic disorder caused by a microdeletion on the 7th chromosome (7q11.23), which includes the gene for elastin (Ewart et al., 1993). WS has an estimated prevalence of 1 in 7500 and an equal sex ratio (Stromme, Bjornstad, & Ramstad, 2002). The syndrome is characterized by atypical facial characteristics (Pober & Dykens, 1996), mild to moderate intellectual delay (Martens, Wilson, & Reutens, 2008), cardiovascular abnormalities (Pober, Johnson, & Urban, 2008), and a hypersociable personality (Doyle, Bellugi,

* Corresponding author at: Department of Psychology, The Ohio State University-Newark, 2012 Founders Hall, 1179 University Dr., Newark, OH 43055, USA. Tel.: +1 740 366 9415; fax: +1 740 366 5047.
*E-mail address:* martens.22@osu.edu (M.A. Martens).

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Korenberg, & Graham, 2004). Despite their typically friendly demeanor, many individuals with WS display anxiety and some also exhibit disruptive behaviors and/or episodes of aggression.

Anxiety is a common feature in the WS behavioral phenotype and occurs in both children and adults (Davies, Udwin, & Howlin, 1998; Dykens, 2003; Einfeld, Tonge, & Rees, 2001; Leyfer, Woodruff-Borden, & Mervis, 2009; Udwin, Howlin, Davies, & Mannion, 1998). Individuals with WS are reported by their parents or caregivers to be more anxious than either chronological age-matched (CA-matched) controls or other individuals with intellectual disabilities (Dimitropoulos, Ho, Klaiman, Koenig, & Schultz, 2009; Dykens & Rosner, 1999; Einfeld, Tonge, & Florio, 1997). It is estimated that as many as 54% of individuals with WS meet criteria for an ICD/DSM diagnosis of anxiety disorder (Stinton, Tomlinson, & Estes, 2012). Individuals with WS are also reported to have specific fears (getting lost, being in a fight, being hit by a car) at a higher rate than others with intellectual disabilities (Dykens, 2003).

Evidence is mixed regarding the degree to which anxiety persists over time in individuals with WS, which may be related to the various methodologies utilized across studies and the type of anxiety being characterized, i.e. generalized anxiety or specific phobias. In a longitudinal study of children and adolescents with WS, 60% had an anxiety disorder diagnosis when initially assessed, based on parents' responses on the Anxiety Disorders Interview Schedule for DSM-IV: Parent version (ADIS-P) (Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010). Although 40% of the participants did not continue to meet diagnostic criteria at the five year follow-up assessment, statistical analyses indicated no age effect; therefore Woodruff-Borden and colleagues suggested that anxiety disorders in individuals with WS persist over time. Adults with WS displayed significantly more fears than children with WS, based on parental report using the Fear Survey Schedule (Dykens, 2003). Dodd and Porter (2009), using parental interview data, reported significantly higher rates of Generalized Anxiety Disorder in adults with WS than in children with WS, but the rates of Specific Phobia were similar between the two groups. Phobias in WS may be impacted by factors that are common in the neurotypical population, such as family history or social reinforcement of fear, as well as by cognitive limitations that may lead to an increased likelihood of fear (Craske, 1999). Significantly lower estimates of anxiety (16.5%) and specific phobias (12%) were found when adults with WS were interviewed using the Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD) (Stinton, Elison, & Howlin, 2010), suggesting anxiety is not a lifelong problem for all individuals with WS.

Despite the variability of evidence regarding the longitudinal course of anxiety in individuals with WS, there is little doubt as to its potentially debilitating effects. Episodes of anxiety may frequently interfere with daily life experiences, thereby impacting the ability of individuals with WS to live as independently as possible. Furthermore, anxiety disorders in neurotypical individuals are associated with medical complications such as cardiac disorders, hypertension, and gastrointestinal problems (Harter, Conway, & Merikangas, 2003), conditions which already impact many individuals with WS (Pober, 2010).

Antidepressant and anxiolytic medications are often used to treat anxiety or depression in the general population (Golden & Nicholas, 2000), as well as in those with intellectual disabilities (Kalachnik, Hanzel, Sevenich, & Harder, 2002). While it is reported that anxiety medications are prescribed for both children and adults with WS (Stinton et al., 2010; Thornton-Wells, Avery, & Blackford, 2011; Woodruff-Borden et al., 2010), no studies of their effectiveness have been published to date. The use of medications which impact serotonin levels may particularly impact individuals with WS given that altered 5-$HT_{1A}$ receptors and increased serotonin metabolism have been noted in the *Gtf2ird1*$^{-/-}$ mouse model of WS, which displays low social anxiety (Proulx, Young, Osborne, & Lambe, 2010; Young et al., 2008).

The behavior and emotional difficulties that are displayed by some individuals with WS include preoccupations, troubled peer relationships, hyperactivity, negative mood, and overall difficulties with social-emotional adjustment (Einfeld et al., 1997, 2001; Gosch & Pankau, 1994; Tomc, Williamson, & Pauli, 1990). Einfeld et al. (2001) noted that these behavioral and emotional difficulties could continue into adulthood.

Use of antipsychotic medication to treat behavioral disturbance in individuals with WS is not well documented in the scientific literature. The only known study documents the use of risperidone in two young adult males with WS, one presenting with aggressive behavior and psychotic symptoms, and the other displaying aggressive behaviors to himself and inappropriate sexual behavior (Savoja & Vicari, 2010). Both patients showed a positive behavioral response to risperidone, but each developed serious gastrointestinal lesions during the course of treatment and the risperidone was discontinued. Following discontinuation of risperidone, the gastrointestinal lesions improved, but the behavioral issues returned.

There is evidence that antipsychotic medications have been used successfully to manage aggressive behaviors in individuals with autism spectrum disorders (McDougle, Stigler, Erickson, & Posey, 2008), but their use among individuals with intellectual disabilities is more controversial. The effectiveness of using antipsychotic medications to reduce challenging behaviors in this population is not well established (Matson, Bielecki, & Mayville, 2003; Matson & Neal, 2009), and there is concern regarding the incidence of adverse side effects (McGillivray & McCabe, 2004). A review of studies examining psychotropic medication use for behavior problems among individuals with intellectual disabilities found that many studies were methodologically flawed, limiting the reliability of the findings (Deb & Unwin, 2007). The impact of antipsychotic medications on individuals with WS is of interest, given their effect on the neurotransmission of serotonin and dopamine (Seeman, 2002). It has been suggested that the dopaminergic system may be impaired in individuals with WS (Gagliardi, Martelli, Burt, & Borgatti, 2007).

To our knowledge, this is the first study to examine parental reports of the effectiveness and side effects of medications used to treat anxiety and behavioral challenges in individuals with WS. Based on the high incidence of psychopathology in this disorder, the purpose was to investigate the prevalence, effectiveness, and side effects of antidepressant, anxiolytic, and antipsychotic medications in individuals who have WS.

## 2. Methods

### 2.1. Participants

A nationwide survey regarding the use and effectiveness of psychotropic medications among individuals with WS was distributed to 2846 members of the Williams Syndrome Association, following institutional IRB approval. A total of 513 parents/caregivers completed the survey regarding their child or adult who has WS.

### 2.2. Survey design

Nearly all participants completed the survey either online at the National Williams Syndrome Conference or in their home, while a few participants completed a paper copy of the survey. The survey included questions regarding the use of SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), other antidepressants and anxiolytics (bupropion, buspirone, venlafaxine, and benzodiazepines clonazapam and lorazepam), and atypical antipsychotic medications (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone). Parents also added in the names of other less-commonly prescribed medications, such as typical antipsychotics. In addition, the survey asked for the age initiated, purpose, duration of use, effectiveness (Helpful, Somewhat Helpful, Not Helpful), and side effects (Behavioral, Gastrointestinal, Metabolic/Physiological, Neurological, Psychological). The survey also asked questions regarding the participants' gender, current age, age when WS was diagnosed, method of WS diagnosis (Genetic test – FISH, Genetic test – Chromosomal microarray, Genetic test – Unknown type, Clinical/Physical features only, Unknown), IQ (Average: 85–115, Borderline/Low Average: 70–84, Mild Intellectual Delay: 55–69, Moderate Intellectual Delay: 40–54, Severe Intellectual Delay: 25–39, Unknown), and ethnicity (Caucasian, Black, Hispanic/Latino, Asian, Native American, Other, Unknown).

In addition, the survey asked whether the individual with WS had ever experienced or currently had the following conditions: *Medical* (Constipation, High blood calcium, Growth problems, Low muscle tone, Joint problems, Dental problems, Frequent ear infections, Eye/vision problems, Hernia, Hearing loss, Sensitive to sound, Early puberty, Kidney problems, Chiari malformation, Acid reflux – GERD, Seizure disorder, Diabetes mellitus, Osteoporosis, Hypothyroidism, Diverticulitis, Scoliosis); *Cardiac-related* (Supravalvular aortic stenosis, Pulmonary artery stenosis, Tetralogy of Fallot, Ventricular septal defect, Aortic valve defect, Mitral valve defect, Coarctation of the aorta, Cardiomyopathy, High blood pressure); *Mental health diagnoses* (Anxiety disorder, Depression, ADHD, Bipolar disorder, Sleep disturbance, Behavior problems, Oppositional defiant disorder, Autism spectrum disorder).

### 2.3. Statistical analysis

Descriptive statistics were calculated overall and for participants reporting the use of the medications listed in the '*Survey design*' section, in addition to other medications noted by the parents. When sample sizes were small or distributions appeared skewed, medians (and interquartile ranges) were used in place of means and standard deviations. Medians were compared using the Wilcoxon rank sum test. Differences in reported rates of psychiatric and medical conditions across groups of medication users were evaluated using Fisher's exact test. To account for multiple testing, Bonferroni adjustments were made within categories of psychiatric and medical conditions. No other analyses were adjusted for multiple comparisons, as analyses were primarily descriptive. Detailed information on medication helpfulness and side effects was examined for medications reported by 10 or more participants. Some participants reported the use of more than one medication, leading to repeated measurements from some subjects. To account for the within-participant correlation of responses, generalized estimating equations with a logit link were used to compare helpfulness of medications within medication categories. This type of analysis accounts for the fact that participants' responses about different medications may be related. Analyses were performed using the SAS System, version 9.1.

Following the overall demographic information, the results of the antidepressant and anxiolytic medications will be presented, followed by the results of the antipsychotic medications. For ease of clarification when results are reported, phrases such as "participants with WS reported," refer to information that was reported via the survey by parents/caregivers of the individuals with WS.

## 3. Results

### 3.1. Demographics of all participants

Table 1 presents the demographic description of the 513 participants with WS. The individuals were predominantly Caucasian (88%) and there were slightly more females than males (55% female). Forty-five percent (45%) of the participants were diagnosed with WS by age 2 years and the majority of participants (75%) were diagnosed by genetic testing. The average age of the participants at survey completion was 17.2 years (SD 11.8), available for 70% of the sample. The age of those who reported being prescribed SSRIs, other antidepressants, anxiolytics, and/or antipsychotics was 22.8 years (SD 11.6, $n = 108/150$), while the mean age of those never taking any of these medications was 14.8 years (SD 11.0, $n = 251/363$).

The prevalence rates of medical conditions that were reported across the lifetime are described in Fig. 1.

**Table 1**
Demographics of all participants.[a]

| | Overall |
|---|---|
| Number of participants | 513 |
| Gender | |
| Male | 45% (233) |
| Female | 55% (280) |
| Age (years) at survey[b] | |
| *n* | 359 |
| Mean (SD) | 17.2 (11.8) |
| Range | 0.6–61 |
| Age at diagnosis | |
| 0–12 months | 26% (134) |
| 13–24 months | 19% (99) |
| 25–48 months | 12% (63) |
| 4–6 years | 8% (42) |
| 7–10 years | 10% (52) |
| 11–13 years | 4% (18) |
| 14–17 years | 5% (25) |
| 18–22 years | 4% (19) |
| 22+ years | 12% (61) |
| How diagnosed | |
| Genetic Test – FISH | 67% (342) |
| Genetic Test – Chromosomal microarray | 3% (13) |
| Genetic Test – Unknown type | 6% (30) |
| Clinical/Physical features only | 25% (126) |
| Unknown | 0% (2) |
| IQ | |
| 85–115 (Average) | 6% (32) |
| 70–84 (Borderline/Low Average) | 23% (120) |
| 55–69 (Mild Intellectual Delay) | 30% (156) |
| 40–54 (Moderate Intellectual Delay) | 11% (56) |
| 25–39 (Severe Intellectual Delay) | 2% (9) |
| Unknown | 27% (140) |
| Race | |
| Caucasian | 88% (449) |
| Black | 2% (8) |
| Hispanic/Latino | 3% (15) |
| Asian | 2% (10) |
| Native American | 0% (2) |
| Other | 5% (26) |
| Unknown | 1% (3) |

[a] Data reported as % (*n*), except where noted.
[b] Available for 359 participants.

### 3.2. SSRIs, other antidepressants, and anxiolytics

#### 3.2.1. Demographics of those taking SSRIs, other antidepressants, or anxiolytics

Twenty-four percent (24%) of the individuals with WS (121/513) had been prescribed at least one SSRI medication, with the vast majority (approximately 92%) indicating that the SSRI was being used to treat symptoms of anxiety. Of the 121 participants who were prescribed an SSRI, 59% were female. At the time the survey was completed, the average age of those taking an SSRI was 23.2 years (SD 11.9), while the average age of non-SSRI users was 15.3 (SD 11.1). The median age that participants reported first taking an SSRI was 15 years. Families reported initiation of SSRI medication as young as age 2 years (1 case), and 37% of those taking an SSRI ($n = 45$) had received at least one trial of SSRI medication by age 12.5 years.

Twelve percent (12%, 62/513) of the participants, 59% female, were prescribed other types of antidepressants or anxiolytics to treat their anxiety symptoms. The average age (at survey completion) of those taking these types of medications was 25.0 years (SD 11.7), range 6–61 years. The youngest age at which a participant was prescribed another type of antidepressant (other than an SSRI) or an anxiolytic was age 4 years.

#### 3.2.2. Use of specific SSRIs, other antidepressants, or anxiolytics

Of the SSRI medications, sertraline was the most prescribed, as reported by 36% (44/121) of SSRI users. Citalopram, fluoxetine, and paroxetine were prescribed at similar rates. As stated in Section 2, detailed analysis was only conducted on medications reported by 10 or more participants. Since only 4 individuals were prescribed fluvoxamine, these data were included in aggregate statistics but not analyzed separately. Bupropion was the only non-SSRI medication to be analyzed separately because it was prescribed to more than 10 participants, while all were included in the aggregate statistics. Anxiolytics were prescribed for 46 of the participants. The most commonly prescribed anxiolytic was the benzodiazepine lorazepam, prescribed for 46% of those taking an anxiolytic (21/46). Buspirone, clonazepam, and lorazepam were analyzed separately, but all anxiolytics were included in the aggregate statistics (see Table 2).

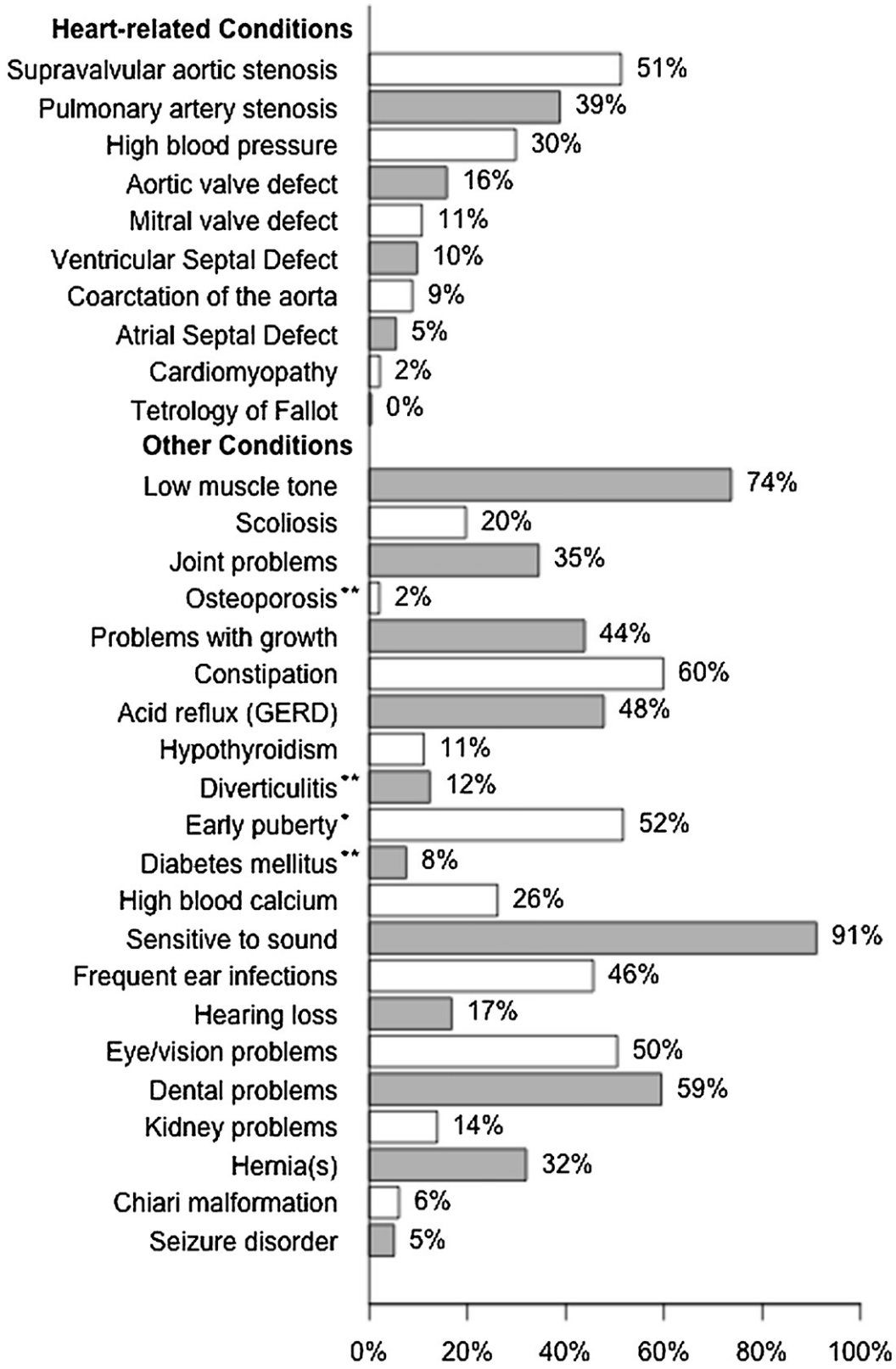


**Fig. 1.** Prevalence of medical conditions. The percentages reflect reported lifetime prevalence rates (ever experienced or currently had) ($n = 513$), except as noted below. *Early puberty: only participants aged 9 or older ($n = 269$). **Osteoporosis, diverticulitis, diabetes mellitus: only participants aged 18 or older ($n = 146$).

**Table 2**
Use of antidepressants and anxiolytics.[a]

| | |
|---|---|
| SSRIs | |
| Number of participants reporting use | 121 |
| Specific SSRIs (% of users) | |
| Citalopram | 31 (26%) |
| Escitalopram | 21 (17%) |
| Fluoxetine | 29 (24%) |
| Fluvoxamine | 4 (3%) |
| Paroxetine | 30 (25%) |
| Sertraline | 44 (36%) |
| Other antidepressants | |
| Number of participants reporting use | 30 |
| Specific antidepressants (% of users) | |
| Amitriptyline | 1 (3%) |
| Bupropion | 11 (37%) |
| Clomipramine | 1 (3%) |
| Desvenlafaxine | 1 (3%) |
| Duloxetine | 1 (3%) |
| Mianserin | 1 (3%) |
| Mirtazapine | 6 (20%) |
| Nortriptyline | 2 (7%) |
| Trazodone | 2 (7%) |
| Venlafaxine | 7 (23%) |
| Anxiolytics | |
| Number of participants reporting use | 46 |
| Specific anxiolytics (% of users) | |
| *Benzodiazepines* | |
| Alprazolam | 6 (13%) |
| Clonazepam | 14 (30%) |
| Diazepam | 4 (9%) |
| Lorazepam | 21 (46%) |
| *Other* | |
| Buspirone | 14 (30%) |

*Note*: 62 participants took other antidepressants or anxiolytics.
[a] Data reported as *n* (%).

### 3.2.3. Helpfulness ratings of SSRIs, other antidepressants, and anxiolytics

Overall, 81% ($n = 98$) of participants who had taken an SSRI indicated that it was either "Helpful" or "Somewhat Helpful" (see Table 3). Helpfulness data did vary depending upon the type of SSRI that was prescribed. Seventy-five to eighty-four percent (75–84%) of those who had taken citalopram, escitalopram, fluoxetine, or sertraline reported that the medication was either "Helpful" or "Somewhat Helpful." In contrast, only 43% of individuals who had taken paroxetine reported it as "Helpful" or "Somewhat Helpful", with 50% indicating that paroxetine was "Not Helpful." The difference in helpfulness between paroxetine vs. the other SSRI medications was statistically significant ($p < 0.001$).

**Table 3**
Helpfulness of antidepressants and anxiolytics used by ten or more participants.[a]

| Medication | Did the medication help? | | | |
|---|---|---|---|---|
| | Yes | Somewhat | No | Unknown |
| SSRIs | | | | |
| Citalopram | 39% (12) | 45% (14) | 13% (4) | 3% (1) |
| Escitalopram | 38% (8) | 38% (8) | 19% (4) | 5% (1) |
| Fluoxetine | 48% (14) | 21% (6) | 21% (6) | 10% (3) |
| Paroxetine | 20% (6) | 23% (7) | 50% (15) | 7% (2) |
| Sertraline | 48% (21) | 27% (12) | 20% (9) | 5% (2) |
| All SSRIs[b] | 49% (59) | 32% (39) | 14% (17) | 5% (6) |
| Other antidepressants and anxiolytics | | | | |
| Bupropion | 55% (6) | 9% (1) | 27% (3) | 9% (1) |
| Buspirone | 21% (3) | 43% (6) | 21% (3) | 14% (2) |
| Clonazepam | 21% (3) | 29% (4) | 43% (6) | 7% (1) |
| Lorazepam | 38% (8) | 33% (7) | 14% (3) | 14% (3) |
| All non SSRI antidepressant/anxiolytics[c] | 45% (28) | 19% (12) | 21% (13) | 15% (9) |

[a] Data reported as % (*n*) where the denominator is the number of participants reporting use of the specific medication.
[b] Includes all SSRIs (including those reported by fewer than ten participants). For participants taking more than one, the highest (best) helpfulness rating is reported.
[c] Includes all non-SSRI antidepressants and anxiolytics (including those reported by fewer than ten participants). For participants taking more than one, the highest (best) helpfulness rating is reported.

**Table 4**
Frequency of side effects for SSRIs used by ten or more participants.[a,b]

| | Citalopram | Escitalopram | Fluoxetine | Paroxetine | Sertraline | Overall[c] |
|---|---|---|---|---|---|---|
| Participants | 31 | 21 | 29 | 30 | 44 | 121 |
| Side effects | | | | | | |
| Behavioral | 10% (3) | 10% (2) | 3% (1) | 13% (4) | 11% (5) | 13% (16) |
| Gastrointestinal | 3% (1) | 5% (1) | 0% (0) | 3% (1) | 5% (2) | 3% (4) |
| Metabolic/Physiological | 13% (4) | 10% (2) | 3% (1) | 10% (3) | 11% (5) | 12% (14) |
| Neurological | 10% (3) | 19% (4) | 14% (4) | 30% (9) | 20% (9) | 22% (27) |
| Psychological | 0% (0) | 0% (0) | 3% (1) | 0% (0) | 0% (0) | 1% (1) |
| Any side effect | 23% (7) | 38% (8) | 21% (6) | 40% (12) | 27% (12) | 34% (41) |

Behavioral includes: Fighting/aggression, Irritable; Gastrointestinal includes: Stomach ache; Metabolic/Physiological includes: Fast heart rate, High blood pressure, Weight gain, Weight loss; Neurological includes: Anxiety, Headache, Muscle tics, Sleep problems, Tremors, Zoned out; Psychological includes: Hallucinations.

[a] Data reported as % (*n*).

[b] See Appendix A for the specific side effects reported within each category.

[c] All SSRIs, including those reported by fewer than ten participants.

Overall, 64% ($n = 40$) of participants reported that other antidepressant or anxiolytic medications were either "Helpful" or "Somewhat Helpful" (see Table 3). Sixty-four percent (64%) of those who had taken bupropion or buspirone indicated that the medication was either "Helpful" or "Somewhat Helpful." Forty-three percent (43%) of those who reported taking clonazepam indicated that the medication was "Not Helpful," compared to only 14% of those taking lorazepam ($p = 0.08$).

### *3.2.4. Side effects of SSRIs, other antidepressants, and anxiolytics: frequency and type*

Table 4 shows the side effects of the SSRIs grouped into the following five categories: Behavioral, Gastrointestinal, Metabolic/Physiological, Neurological, and Psychological. Appendix A displays the specific SSRI side effect data within each category reported by participants. Overall, 34% of SSRI users ($n = 41$) reported experiencing one or more side effects with an SSRI medication. Across all the SSRIs, the most common specific side effects reported were Irritability (12%), Appearing "zoned" (7%), Sleep problems (6%), Headache (6%), and Tremors (5%).

Anxiety was also noted as a side effect for 9% of the participants overall, but this percentage was mostly influenced by those taking paroxetine, reported by 23% ($n = 7$) (see Appendix A). The report of increased anxiety for those taking paroxetine may reflect a negative side effect of this particular medication. Alternately, it may indicate that the underlying symptom of anxiety was not being treated effectively, as evidenced by paroxetine's lowered helpfulness rating compared to the other SSRI medications (previously reported in the Section 3.2.3).

From 21 to 27% of those who took fluoxetine, citalopram, and sertraline reported at least one side effect, whereas 38–40% of those who took paroxetine or escitalopram noted a side effect. Neurological side effects were the most frequently reported for escitalopram, fluoxetine, paroxetine, and sertraline, while the side effects for citalopram did not appear to cluster in a particular category.

There was no significant difference between males and females in terms of specific side effects or category of side effects. When comparing medications, differences in the percent reporting side effects was also not statistically significant, although power to detect significant differences was limited by the small numbers of participants reporting each side effect.

Table 5 shows the side effects of the other antidepressants and anxiolytics grouped into categories. Appendix B displays the specific side effect data within each category for the other antidepressants and anxiolytics as reported by participants. The most common side effects for the other antidepressants and anxiolytics were in the neurological category. Bupropion was reported to have the least number of side effects, though the number reporting side effects were small and differences in percent experiencing side effects were not significant.

**Table 5**
Side effects for other antidepressants/anxiolytics used by ten or more participants.[a,b]

| | Bupropion | Buspirone | Clonazepam | Lorazepam | Overall[c] |
|---|---|---|---|---|---|
| Participants | 11 | 14 | 14 | 21 | 62 |
| Side effects | | | | | |
| Behavioral | 9% (1) | 7% (1) | 14% (2) | 0% (0) | 8% (5) |
| Gastrointestinal | 9% (1) | 7% (1) | 0% (0) | 0% (0) | 3% (2) |
| Metabolic/Physiological | 0% (0) | 7% (1) | 0% (0) | 5% (1) | 5% (3) |
| Neurological | 0% (0) | 29% (4) | 36% (5) | 19% (4) | 23% (14) |
| Psychological | 0% (0) | 0% (0) | 0% (0) | 5% (1) | 2% (1) |
| Any side effect | 9% (1) | 29% (4) | 36% (5) | 29% (6) | 30% (19) |

Behavioral includes: Fighting/aggression, Irritable; Gastrointestinal includes: Stomach ache; Metabolic/Physiological includes: Fast heart rate, Weight gain, Weight loss; Neurological includes: Anxiety, Sleep problems, Tremors, Zoned out; Psychological includes: Hallucinations.

[a] Data reported as % (*n*).

[b] See Appendix B for the specific side effects reported within each category.

[c] All other (non-SSRI) antidepressants and anxiolytics.

**Table 6**
Psychiatric and medical conditions reported by those who had been prescribed SSRIs, other antidepressants and anxiolytics, antipsychotics, and no psychotropic medications.[a]

| Ever experienced/had... | SSRI users ($n = 121$) | Other antidepressant/anxiolytics users ($n = 62$) | Antipsychotics users ($n = 53$) | No psychotropic medication ($n = 363$) |
|---|---|---|---|---|
| Psychiatric conditions | | | | |
| Anxiety disorder | 92% (111)*** | 85% (53)*** | 96% (51)*** | 23% (84) |
| Depression | 51% (62)*** | 56% (35)*** | 49% (26)*** | 4% (14) |
| ADHD | 47% (57)** | 34% (21) | 58% (31)*** | 25% (92) |
| Bipolar disorder | 7% (8)* | 15% (9)*** | 13% (7)** | 1% (3) |
| Sleep disturbance | 49% (59)*** | 48% (30)* | 55% (29)** | 25% (92) |
| Behavior problems | 57% (69)*** | 47% (29)*** | 75% (40)*** | 17% (61) |
| Oppositional defiant disorder | 14% (17)*** | 15% (9)* | 25% (13)*** | 2% (8) |
| Autism spectrum disorder | 12% (15)* | 10% (6) | 21% (11)* | 4% (16) |
| Medical conditions | | | | |
| Constipation | 73% (88)* | 68% (42) | 70% (37) | 56% (203) |
| Joint problems | 48% (58)* | 45% (28) | 53% (28)* | 29% (105) |
| Dental problems | 71% (86)* | 58% (36) | 68% (36) | 55% (199) |
| Diabetes mellitus | 11% (13)* | 6% (4) | 6% (3) | 2% (7) |
| Scoliosis | 31% (37)* | 32% (20)* | 26% (14) | 15% (54) |

[a] Data reported as % ($n$). Groups are not mutually exclusive, since participants could report multiple types of psychotropic medications.
* $p < 0.05$ for comparison with no psychotropic medication group. Fisher's exact test, Bonferroni-adjusted within category (comorbid conditions: 8 tests, significant medical conditions: 21 tests).
** $p < 0.001$ for comparison with no psychotropic medication group.
*** $p < 0.0001$ for comparison with no psychotropic medication group.

*3.2.5. Psychiatric and medical conditions reported by those who had been prescribed SSRIs, other antidepressants, or anxiolytics*

As expected, the individuals who were prescribed SSRIs were significantly more likely than non-SSRI users to be diagnosed with at least one of the following psychiatric disorders: Anxiety disorder, Depression, ADHD, Bipolar disorder, Sleep disturbance, Behavior problems, Oppositional defiant disorder, Autism spectrum disorder ($p$ values range from $<0.0001$ to 0.03) (see Table 6). Similarly, those who were prescribed other antidepressants or anxiolytics were significantly more likely than other participants to be diagnosed with at least one of the following psychiatric disorders: Anxiety disorder, Depression, Bipolar disorder, Sleep disturbance, Behavior problems, Oppositional defiant disorder ($p$ values range from $<0.0001$ to 0.003). Of the 213 participants who had been diagnosed with an anxiety disorder, 61% ($n = 129$) had been prescribed at least one SSRI, other antidepressant, or anxiolytic, while the other 39% ($n = 84$) had not been prescribed any of these medications.

When considering medical conditions endorsed by those who had been prescribed an SSRI, it is important to keep in mind that we do not know the age at which the medical condition was diagnosed, how long it persisted, and whether or not the timing of the diagnosis coincided with the initiation of an SSRI. Therefore, it is important to be cautious when interpreting the following statistical results. Those who had been prescribed SSRIs were significantly more likely to report current or past experiences of at least one of the following medical conditions compared to those who did not take any of the psychotropic medications that were examined in this survey: Diabetes mellitus, Constipation, Joint problems, Scoliosis, and Dental problems (see Table 6 and detailed below). The same health problems (except for dental problems) were endorsed when those who had been prescribed an SSRI were asked about current medical conditions only. Those who had been prescribed other antidepressants or anxiolytics were significantly more likely to report scoliosis ($p = .04$) compared to those who had not been prescribed any psychotropic medications.

Eleven percent (11%, 13/121) of participants who had been prescribed an SSRI reported diabetes mellitus, compared to 2% (8/392) of those taking none of the psychotropic medications ($p = 0.003$). We did not collect information on whether the diabetes was Type 1 or Type 2. When the analysis was limited to participants aged 20+ ($n = 140$), then diabetes was reported in 16% (8/50) of SSRI users and 3% (3/90) of non-SSRI users. The individuals who also reported a diagnosis of diabetes were not prescribed one particular SSRI over another. Those who had been prescribed an SSRI were also more likely to report constipation ($p = 0.03$), joint problems ($p = 0.005$), scoliosis ($p = 0.005$), and dental problems ($p = 0.04$) than those not taking any medication for anxiety, depression, or behavior problems.

## *3.3. Antipsychotic medications*

*3.3.1. Demographics of those taking antipsychotics*

Overall, 10% of the survey participants ($n = 53$) indicated that they had taken an antipsychotic medication. The average age (at survey completion) of those who were taking or had taken an antipsychotic medication was 21.4 years (SD 11.5), compared to an average age of 16.7 years (SD 11.7) for those who had not been prescribed an antipsychotic medication. The youngest age that a child was reported to have taken an antipsychotic was age two years (1 case). Fifty-three percent (53%) of those who had been prescribed an antipsychotic medication were female. Forty-three percent (43%, $n = 23$) had received at least one trial of antipsychotic medication use by age 12.5 years.

**Table 7**
Use of antipsychotic medications.[a]

| | |
|---|---|
| Antipsychotics | |
| Number of participants reporting use | 53 |
| Specific antipsychotics (% of users) | |
| *Atypical antipsychotics* | |
| Aripiprazole | 18 (34%) |
| Clozapine | 1 (2%) |
| Olanzapine | 9 (17%) |
| Quetiapine | 16 (30%) |
| Risperidone | 34 (64%) |
| Ziprasidone | 3 (6%) |
| *Typical antipsychotics* | |
| Chlorpromazine | 1 (2%) |
| Haloperidol | 1 (2%) |
| Thioridazine | 1 (2%) |
| *Other behavior medications* | |
| Gabapentin | 1 (2%) |
| Naltrexone | 4 (8%) |
| Valproic acid | 3 (6%) |

[a] Data reported as *n* (%).

### 3.3.2. Use of specific antipsychotics

Table 7 shows that the most prescribed antipsychotic medication was risperidone, reported by 64% ($n = 34$) of those taking an antipsychotic medication. Other commonly prescribed antipsychotics were aripiprazole and quetiapine.

### 3.3.3. Helpfulness ratings of antipsychotics

The helpfulness data for the three antipsychotic medications reported by 10 or more participants is found in Table 8. There was a significant difference in helpfulness for aripiprazole compared to quetiapine and risperidone ($p = 0.04$). Sixty-nine percent (69%) of those who had been prescribed quetiapine, and 68% of those who had been prescribed risperidone, reported that these medications were either "Helpful" or "Somewhat Helpful." In contrast, only 39% of those prescribed aripiprazole reported that this medication was either "Helpful" or "Somewhat Helpful," with the majority (56%) indicating that aripiprazole was "Not Helpful."

### 3.3.4. Side effects of antipsychotics: frequency and type

Table 9 lists the side effects of the antipsychotic medications grouped into the following categories: Behavioral, Gastrointestinal, Metabolic, Neurological, and Psychological. Appendix C shows the specific side effects within each category reported by these participants. Overall, 58% of those taking an antipsychotic medication ($n = 31$) reported experiencing at least one side effect. Across all antipsychotic medications, the most common specific side effects were Weight gain (28%), Irritability (25%), Stomach ache (23%), Tremors (23%), and Fighting/aggression (21%).

Neurological side effects were the most frequently reported for aripiprazole and quetiapine. Although the olanzapine results were not included in the side effect data because the sample size was less than 10 ($n = 9$), it was noted that weight gain was reported particularly for those who had been prescribed olanzapine (44%), compared to 6% who reported weight gain after taking aripiprazole or quetiapine, and 21% who reported weight gain after taking risperidone. Overall, females reported more neurological side effects than males (50% compared to 24%), but the influence of gender on side effects was not statistically significant, most likely due to the small number of participants reporting each medication. The frequency of side effects between antipsychotic medications was also not statistically significant.

### 3.3.5. Psychiatric and medical conditions reported by those who had been prescribed antipsychotic medications

As expected, the individuals who were prescribed an antipsychotic medication were significantly more likely to be diagnosed with at least one of the following psychiatric conditions compared to those not prescribed antipsychotics: Anxiety

**Table 8**
Helpfulness of antipsychotic medications used by ten or more participants.[a]

| Medication | Did the medication help? | | | |
|---|---|---|---|---|
| | Yes | Somewhat | No | Unknown |
| Antipsychotics | | | | |
| Aripiprazole | 28% (5) | 11% (2) | 56% (10) | 6% (1) |
| Quetiapine | 31% (5) | 38% (6) | 31% (5) | 0% (0) |
| Risperidone | 32% (11) | 35% (12) | 26% (9) | 6% (2) |
| All antipsychotics[b] | 40% (21) | 32% (17) | 23% (12) | 6% (3) |

For participants taking more than one, the highest (best) helpfulness rating is reported.
[a] Data reported as % (*n*) where the denominator is the number of participants reporting use of the specific medication.
[b] Includes all antipsychotic medications (including those reported by fewer than ten participants).

**Table 9**
Frequency of side effects for antipsychotic medications used by ten or more participants.[a,b]

| | Aripiprazole | Quetiapine | Risperidone | Overall[c] |
|---|---|---|---|---|
| Participants | 18 | 16 | 34 | 53 |
| Side effects | | | | |
| Behavioral | 22% (4) | 13% (2) | 9% (3) | 30% (16) |
| Gastrointestinal | 11% (2) | 6% (1) | 6% (2) | 23% (12) |
| Metabolic | 11% (2) | 6% (1) | 21% (7) | 30% (16) |
| Neurological | 28% (5) | 31% (5) | 18% (6) | 40% (21) |
| Psychological | 0% (0) | 6% (1) | 0% (0) | 8% (4) |
| Any side effect | 39% (7) | 44% (7) | 35% (12) | 58% (31) |

Behavioral includes: Fighting/aggression, Irritable; Gastrointestinal includes: Constipation, Stomach ache; Metabolic includes: Weight gain, Weight loss; Neurological includes: Fainting, Headache, Muscle tics, Seizures, Sleep problems, Tremors, Unusual movements, Zoned out; Psychological includes: Hallucinations, Suicidal thoughts.

[a] Data reported as % (*n*).

[b] See Appendix C for the specific side effects reported within each category.

[c] All antipsychotic medications, including those reported by fewer than ten participants.

disorder, Depression, ADHD, Bipolar disorder, Sleep disturbance, Behavior problems, Oppositional defiant disorder, Autism spectrum disorder ($p$ values range from $<0.0001$ to 0.001). Those who were prescribed an antipsychotic medication were significantly more likely to report joint problems that those not taking any psychotropic medications for anxiety, depression, or behavior problems (see Table 6).

## 4. Discussion

This comprehensive survey study of antidepressant, anxiolytic, and antipsychotic medication usage in individuals who have WS is the largest to date and describes the reported helpfulness and side effects that are associated with these types of medications, in addition to psychiatric and medical conditions endorsed (current or in the past) by medication users. In summary, 81% of those taking an SSRI reported it to be either "Helpful" or "Somewhat Helpful", 64% of those taking another form of antidepressant or anxiolytic medication reported it to be either "Helpful" or "Somewhat Helpful", and 72% of those taking an antipsychotic medication reported it to be either "Helpful" or "Somewhat Helpful". A summary of the side effect data indicates that 34% reported some type of side effect when taking an SSRI, 30% reported some type of side effect when taking another form of antidepressant or anxiolytic medication, and 58% reported some type of side effect when taking an antipsychotic medication. It is important to note that the side effect and helpfulness data should be interpreted with caution given that some people who report their reaction to a particular medication may be receiving more medication, or taking multiple medications, compared to others. The findings will be discussed in more detail in the following sections: Sections 4.1–4.3.

### *4.1. SSRIs*

Our results indicate that 24% of the participants were prescribed at least one SSRI for anxiety or depression, although there is evidence that anxiety disorders may be evident in more than 50% of individuals with WS (Woodruff-Borden et al., 2010). In neurotypical children and adolescents presenting with depression, SSRIs are prescribed more than 50% of the time during outpatient visits (Ma, Lee, & Stafford, 2005). It is not known whether other treatment strategies for anxiety are being prescribed to individuals with WS, such as environmental management or cognitive-behavioral therapy, or whether the reduced rate of SSRI usage reflects uncertainty by parents and/or physicians about the effectiveness and safety of these medications in individuals with WS.

The results of the 'Helpfulness' data indicate that paroxetine was rated the least helpful SSRI in treating symptoms of anxiety in individuals with WS when compared to the other SSRIs. There was no significant difference between the helpfulness ratings of citalopram, escitalopram, fluoxetine, and sertraline. The most common side effects reported as a result of taking an SSRI (irritability, sleep problems, headache, tremors, and appearing "zoned") are among those noted by neurotypical individuals (Hetrick, Merry, Mckenzie, Sindahl, & Proctor, 2007), although not to the same degree. Survey participants reported neurological and behavioral side effects from taking SSRIs, and it has been reported that typical dosages of SSRIs in adults with WS can be associated with an increased risk of behavioral difficulties (Cherniske et al., 2004). Gastrointestinal difficulties are the most common side effect noted in neurotypical individuals (Goldstein & Goodnick, 1998) and while only a small percentage of individuals with WS reported stomach problems as a result of taking an SSRI, a majority did report constipation. The use of antidepressant medications is also associated with increased risk of suicidal ideation in neurotypical children and adolescents (Hetrick et al., 2007). Although not listed as a specific possible side effect on the WS survey, participants had the opportunity to report any additional side effects and none indicated suicidal thoughts as a side effect of taking an SSRI.

As stated previously, the results of medical conditions (past or present) that were endorsed by those who had been prescribed an SSRI medication should be interpreted cautiously, since we cannot determine when a particular medication

was initiated in relation to when a medical diagnosis was given. It is also important to keep in mind that the survey participants who reported taking an SSRI were older than those who did not endorse taking an SSRI, so our findings may also be influenced in part by age. Our results indicate that those who had been prescribed an SSRI were significantly more likely to report a diagnosis of diabetes mellitus than those not taking any medication for anxiety, depression, or behavior problems. It has been reported that long-term use (>24 months) of moderate to high doses of SSRIs in neurotypical individuals is associated with an increased risk of diabetes mellitus (Andersohn, Schade, Suissa, & Garbe, 2009). The use of SSRIs has been shown to significantly increase the risk of diabetes either on their own (Rubin et al., 2008) or when taken concurrently with tricyclic antidepressants (Brown, Majumdar, & Johnson, 2008). Evidence is mixed as to whether specific SSRIs are more likely to be associated with risk factors associated with diabetes (Jindal, 2009; Raeder, Bjelland, Vollset, & Steen, 2006). In our study, those with diabetes were not more likely to have been prescribed one SSRI over another.

It is also essential to keep in mind that physical health problems can precede mental health problems. A longitudinal modeling study of neurotypical individuals found that those who reported diabetes mellitus were more likely to have taken SSRIs compared to those who did not. Importantly, this group difference was evident not only after diagnosis of diabetes, but also before the diagnosis (Kivimaki et al., 2010). Kivimaki and colleagues suggest that more research needs to be done to determine if there is a causal pathway between SSRI use and diabetes.

Pober and colleagues conducted a study of 28 adults with WS (age range 30–52 years) who had not previously been diagnosed with either diabetes or impaired glucose levels (pre-diabetes) (Pober et al., 2010). They found that 35% of their sample met criteria for diabetes, while an additional 39% showed impaired glucose intolerance. Pober and colleagues acknowledged that some of their participants were taking medications that have been associated with diabetes mellitus (beta-blockers and the atypical antipsychotic olanzapine). Only three of the SSRI users in our study who had diabetes also reported taking an antipsychotic medication, while one additional participant reported the use of a beta-blocker. It is also important to note that 50% of the participants in the Pober et al. study were taking SSRIs, although it was not reported if there was an association between those taking SSRIs and the prevalence of diabetes or pre-diabetes.

Two genes mapping to the WS chromosome region – syntaxin-1A (STX-1A) and MLXIPL – have been implicated in abnormalities of glucose metabolism (Antonell, Vilardell, & Pɛrez Jurado, 2010; Chen, Bruederle, Gaisano, & Shyng, 2011; Somanath, Barg, Marshall, Silwood, & Turner, 2009). This inborn potential for problems with glucose metabolism, combined with the use of medications known to carry an increased risk of promoting diabetes, suggests that use of SSRI medications in individuals with WS should be carefully monitored. It would be important for future WS research to consider the age that SSRI use begins and the age that impaired glucose levels are noted in order to further examine this relationship.

Our study results indicate that those who had been prescribed SSRIs were significantly more likely to report constipation than the survey participants taking no psychotropic medications. Constipation is a frequent complaint among individuals with WS, affecting 40% of infants, children, and adults (American Academy of Pediatrics, 2001). There is also recent evidence suggesting that bowel problems may increase with age in individuals with WS (Elison, Stinton, & Howlin, 2010), so we have to consider that this significant relationship might be related to age rather than SSRI use. Research in the neurotypical population suggests that approximately 10% of individuals who take an SSRI report constipation as a side effect (Trindade, Menon, Topfer, & Coloma, 1998). It is possible that the risk of constipation as a potential side effect of an SSRI medication may be increased in individuals with WS due to their predisposition to this gastrointestinal condition; therefore we suggest that individuals with WS who take SSRIs be carefully monitored and treated for any signs of constipation.

We found that individuals with WS who had been prescribed an SSRI were significantly more likely to report joint problems or scoliosis compared to those not taking a psychotropic medication. The medical literature notes that joint abnormalities and scoliosis are quite common in both children and adults with WS (American Academy of Pediatrics, 2001), with gene variability in elastin metabolism attributed to both of these medical issues (Morris et al., 2010). Recent research indicates that joint contractures may worsen with age in WS (Pober, 2010). Although those who had been prescribed an SSRI were older than those who had never taken an SSRI (23 years vs. 15 years), they were still fairly young. Further research is indicated in order to investigate the relationship between musculoskeletal abnormalities, SSRI usage, and age among individuals with WS.

Our results also show that individuals who were prescribed an SSRI were significantly more likely to report dental problems than those not taking a psychotropic medication. SSRIs may produce a reduction in saliva and change its composition by impacting the blood flow of the salivary glands (de Almeida et al., 2008; Schubert & Izutsu, 1987). While the nature of the dental problems was not specified, dry mouth can increase the likelihood of oral infections, such as dental caries (Nagler, 2004).

### 4.2. Other antidepressants and anxiolytics

Our survey results indicate that 12% of the survey participants were prescribed other types of antidepressants or anxiolytics to treat their symptoms of depression or anxiety. Bupropion was the most commonly prescribed other antidepressant, lorazepam was the most prescribed benzodiazepine, and buspirone was the most commonly prescribed anxiolytic.

Over half of bupropion users reported that the medication was "Helpful," while less than one quarter of buspirone users reported that it was "Helpful." It should be noted that bupropion and buspirone do not impact the same neurotransmitters. Bupropion inhibits the reuptake of norepinephrine and dopamine (Stahl et al., 2004), while buspirone is a partial agonist for the serotonin 5-$HT_{1A}$ receptor (Blier, Bergeron, & de Montigny, 1997). These medications may differentially impact the WS

genotype given that serotonin is metabolized at an increased rate and 5-$HT_{1A}$ receptors are altered in the *Gtf2ird1*$^{-/-}$ mouse model of WS (Proulx et al., 2010; Young et al., 2008). It is also important to be aware that bupropion lowers the threshold for seizures, therefore caution is suggested when prescribing bupropion to children with intellectual disabilities due to their heightened risk of seizures (Handen & Gilchrist, 2006; McDermott et al., 2005).

There was a trend toward higher helpfulness ratings for lorazepam than clonazepam. A fairly high percentage of survey participants indicated that clonazepam was not helpful (43%). The literature on the effectiveness of clonazepam is mixed. There is evidence that clonazepam can be helpful in reducing panic attacks in typically developing individuals (Nardi & Perna, 2006; Tesar et al., 1991), but research also indicates that clonazepam may not beneficial in reducing anxiety in typical children with separation anxiety disorders (Graae, Milner, Rizzotto, & Klein, 1994).

The participants who were prescribed buspirone reported more side effects than those taking bupropion. The majority of the side effects for buspirone appeared to be neurological in nature (anxiety, sleep problems, feeling "zoned out"), whereas the most common side effects of buspirone in neurotypical individuals include dizziness and nausea (Davidson, DuPont, Hedges, & Haskins, 1999). Few side effects were reported by the individuals with WS who were prescribed bupropion, which is consistent with the literature on side effects of bupropion in neurotypical individuals (Fava et al., 2005). It has also been reported that bupropion may exacerbate tics in children who are diagnosed with ADHD (Spencer, Biederman, Steingard, & Wilens, 1993). This potential side effect should certainly be monitored in individuals with WS, who have a fairly high rate of ADHD symptoms (Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006).

Those who were prescribed the benzodiazepines clonazepam and lorazepam reported neurological side effects, including feeling "zoned out" and anxious. Clonazepam and lorazepam have been shown to produce adverse behavioral side effects in individuals with intellectual disabilities, including aggression, irritability, and disinhibition (Kalachnik et al., 2002), and there are concerns about paradoxical reactions and rebound effects in the typical population (Mancuso, Tanzi, & Gabay, 2004; Scharf & Jacoby, 1982).

### 4.3. Antipsychotics

Ten percent (10%) of the survey participants reported taking an antipsychotic medication, with risperidone the most commonly prescribed. The majority of the participants who had taken risperidone or quetiapine indicated that the medication was beneficial, while aripiprazole was reported to be the least helpful antipsychotic medication. In typical children and adolescents, risperidone, quetiapine, and aripiprazole demonstrate similar rates of effectiveness in treating aggression, tantrums, and manic episodes (Vitiello et al., 2009). In children and adults with an autism spectrum disorder, risperidone and aripiprazole appear to be the most effective in reducing compulsive behavior and irritability (Masi et al., 2009; McDougle et al., 1998, 2008). Aripiprazole was found to be effective in reducing aggression and moodiness in children who had an intellectual disability but no features of autism (Valicenti-McDermott & Demb, 2006).

Our current findings suggest that aripiprazole is not as effective as either risperidone or quetiapine in treating behavioral disturbance in individuals with WS. These findings may be associated with the difference between medications in terms of whether they are increasing or decreasing serotonin and dopamine levels. Whereas risperidone and quetiapine are antagonists for serotonin and dopamine (Richelson & Souder, 2000; Schatzberg & Nemeroff, 2009), aripiprazole is a partial agonist for both of these neurotransmitters, and in particular impacts the serotonergic 5-$HT_{1A}$ receptor. It is also an antagonist at serotonin 2A receptors and an antagonist at dopamine 2 receptors at higher doses (Burstein et al., 2005; Jordan et al., 2002).

The use of antipsychotic medication in individuals with WS is not well documented in the scientific literature. The only published study to date reports on the use of risperidone in two male subjects (20 and 22-year old) presenting with psychotic symptoms (Savoja & Vicari, 2010). Both subjects developed significant maladaptive behaviors, such as aggression and inappropriate sexual behavior. Both responded favorably to risperidone treatment but developed severe gastrointestinal (GI) inflammatory or ulcerative side effects including grade B esophagitis (mucosal break $>5$ mm) and gastroduodenal ulcer. Risperidone treatment was suspended upon which the GI symptoms improved but psychotic behaviors returned. A recent study of typical individuals has also suggested an association between antipsychotic drugs and gastrointestinal bleeding (Verdel et al., 2011), providing further evidence that individuals with WS who are taking any antipsychotic medications should be carefully monitored in order to detect early warning signs of adverse GI-related side effects.

### 4.4. Limitations

This initial study of antidepressant, anxiolytic, and antipsychotic medication usage among individuals with WS does have limitations that should be noted. We recognize that survey data may be prone to response bias and therefore our results may not accurately represent the percentage of individuals with WS who have taken any of these medications. In addition, effectiveness was measured by parental report using terms that may have subjective definitions, and was not based on standardized pre- or post-questionnaires or rating scales. Some of the survey participants may have also received psychosocial interventions as well as pharmacological treatment for their anxiety or behavior issues. Our survey method did not allow for the measurement of dosage effects, titration of drug dosage, and duration of drug treatment, and we believe that these issues warrant additional study given anecdotal evidence that individuals with WS are more sensitive than average to neurotypical medication dosages (Cherniske et al., 2004; Pober, 2010). We believe it would also be important for future studies to examine how many individuals with WS stop taking psychotropic medications and their reasons for stopping.

It is important to acknowledge that behavior management can be beneficial in treating childhood anxiety and behavior disorders and may be helpful in individuals with WS (Einfeld et al., 2001). There is evidence that behavioral relaxation, modeling, and desensitization can be beneficial in reducing anxiety in individuals with intellectual disabilities (Erfanian & Miltenberger, 1990; Lindsay, Fee, Michie, & Heap, 1994; Luscre & Center, 1996; Matson, 1981). Multi-site controlled studies are needed in order to investigate the effectiveness of pharmacological therapy, alone and in combination with cognitive behavioral therapy, in individuals with WS.

Our findings highlight the need for additional studies of medication usage in individuals with WS utilizing standardized questionnaires, including a self-report measure and a review of medical records, in order to address the critical need of treating anxiety and behavior challenges in these individuals and take into consideration the positive and negative aspects of specific medications. Furthermore, a critical evaluation of medication dosages is necessary in order to better evaluate the benefits and side effects of particular medications, specifically those that affect serotonin levels. These studies will enhance our understanding of how pharmacological treatments can be utilized to improve the quality of life in individuals with WS.

## Appendix A

Specific side effects for SSRI use in individuals with Williams syndrome.[a]

| | Citalopram | Escitalopram | Fluoxetine | Paroxetine | Sertraline | All SSRIs[b] |
|---|---|---|---|---|---|---|
| Participants | 31 | 21 | 29 | 30 | 44 | 121 |
| Behavioral | | | | | | |
| Fighting | 3% (1) | – (0) | – (0) | 3% (1) | 7% (3) | 4% (5) |
| Irritability | 10% (3) | 10% (2) | 3% (1) | 13% (4) | 7% (3) | 12% (14) |
| Gastrointestinal | | | | | | |
| Stomach ache | 3% (1) | 5% (1) | – (0) | 3% (1) | 5% (2) | 3% (4) |
| Metabolic/Physiological | | | | | | |
| Fast HR | 6% (2) | – (0) | 3% (1) | – (0) | 2% (1) | 2% (3) |
| High BP | 6% (2) | – (0) | – (0) | – (0) | 7% (3) | 4% (5) |
| Weight gain | 3% (1) | 10% (2) | – (0) | 7% (2) | 2% (1) | 5% (6) |
| Weight loss | – (0) | – (0) | – (0) | 3% (1) | – (0) | 1% (1) |
| Neurological | | | | | | |
| Anxiety | 3% (1) | 5% (1) | 3% (1) | 23% (7) | 5% (2) | 9% (11) |
| Headache | 3% (1) | 5% (1) | 3% (1) | 3% (1) | 7% (3) | 6% (7) |
| Muscle tics | 3% (1) | – (0) | – (0) | 7% (2) | 2% (1) | 2% (3) |
| Sleep problems | 3% (1) | 5% (1) | 7% (2) | 3% (1) | 2% (1) | 6% (7) |
| Tremors | 3% (1) | 10% (2) | – (0) | 10% (3) | 2% (1) | 5% (6) |
| Zoned out | 3% (1) | 5% (1) | 3% (1) | 7% (2) | 7% (3) | 7% (8) |
| Psychological | | | | | | |
| Hallucinations | – (0) | – (0) | 3% (1) | – (0) | – (0) | 1% (1) |

[a] Data reported as % (*n*).
[b] All SSRIs, including those reported by fewer than ten participants.

## Appendix B

Specific side effects for other antidepressants and anxiolytics in individuals with Williams syndrome.[a]

| | Bupropion | Buspirone | Clonazepam | Lorazepam | All non-SSRI antidepressants and anxiolytics[b] |
|---|---|---|---|---|---|
| Pariticpants | 11 | 14 | 14 | 21 | 63 |
| Behavioral | | | | | |
| Fighting | – (0) | 7% (1) | 7% (1) | – (0) | 3% (2) |
| Irritability | 9% (1) | – (0) | 14% (2) | – (0) | 6% (4) |
| Gastrointestinal | | | | | |
| Stomach ache | 9% (1) | 7% (1) | – (0) | – (0) | 3% (2) |
| Metabolic/Physiological | | | | | |
| Fast HR | – (0) | 7% (1) | – (0) | – (0) | 2% (1) |
| Weight gain | – (0) | – (0) | – (0) | 5% (1) | 2% (1) |
| Weight loss | – (0) | 7% (1) | – (0) | – (0) | 3% (2) |
| Neurological | | | | | |
| Anxiety | – (0) | 14% (2) | 14% (2) | 5% (1) | 6% (4) |
| Sleep problems | – (0) | 7% (1) | – (0) | 5% (1) | 5% (3) |
| Tremors | – (0) | – (0) | 7% (1) | 5% (1) | 5% (3) |
| Zoned out | – (0) | 7% (1) | 29% (4) | 14% (3) | 14% (9) |
| Psychological | | | | | |
| Hallucinations | – (0) | – (0) | – (0) | 5% (1) | 2% (1) |

[a] Data reported as % (*n*).
[b] All other (non-SSRI) antidepressants and anxiolytics, including those reported by fewer than ten participants.

## Appendix C

Specific side effects for antipsychotic medications in individuals with Williams syndrome.[a]

| | Aripiprazole | Quetiapine | Risperidone | All antipsychotic medications[b] |
|---|---|---|---|---|
| Participants | 18 | 16 | 34 | 53 |
| Behavioral | | | | |
| Fighting | 17% (3) | 6% (1) | 6% (2) | 21% (11) |
| Irritability | 17% (3) | 13% (2) | 9% (3) | 25% (13) |
| Gastrointestinal | | | | |
| Constipation | 6% (1) | – (0) | – (0) | 2% (1) |
| Stomach ache | 11% (2) | 6% (1) | 6% (2) | 23% (12) |
| Metabolic/Physiological | | | | |
| Weight gain | 6% (1) | 6% (1) | 21% (7) | 28% (15) |
| Weight loss | 6% (1) | – (0) | – (0) | 4% (2) |
| Neurological | | | | |
| Fainting | 6% (1) | – (0) | – (0) | 2% (1) |
| Headache | 11% (2) | 13% (2) | – (0) | 19% (10) |
| Muscle tics | 11% (2) | 6% (1) | 3% (1) | 9% (5) |
| Seizures | – (0) | – (0) | 3% (1) | 2% (1) |
| Sleep problems | 11% (2) | – (0) | 6% (2) | 17% (9) |
| Tremors | 11% (2) | 25% (4) | 12% (4) | 23% (12) |
| Unusual movements | 11% (2) | 13% (2) | 3% (1) | 11% (6) |
| Zoned out | – (0) | 6% (1) | – (0) | 2% (1) |
| Psychological | | | | |
| Hallucinations | – (0) | 6% (1) | – (0) | 9% (5) |
| Suicidal thoughts | – (0) | 6% (1) | – (0) | 8% (4) |

[a] Data reported as % (*n*).
[b] All antipsychotic medications, including those reported by fewer than ten participants.

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