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

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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,

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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.