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Psychiatric Diagnoses and Treatment in Wolfram Syndrome

Angela M. Reiersen, MD, MPE[1] Anagha Narayanan, BA[1] Richa A. Sinkre[1] Tamara Hershey, PhD[1,2]

Departments of [1]Psychiatry & [2]Radiology, Washington University in St. Louis School of Medicine

Washington University in St. Louis School of Medicine

MIR Mallinckrodt Institute of Radiology

Wolfram Syndrome (DIDMOAD)

WFS1 gene: codes for wolframin protein

WFS1 pathogenic variants can lead to:

- •Diabetes Insipidus (DI)
- •Diabetes Mellitus (DM)
- •Optic Atrophy (OA)
- •Deafness (D)

Other features (under investigation):

- Progressive neurological dysfunction (balance problems, swallowing difficulties)
- Sleep problems (including sleep apnea), fatigue, and psychiatric disorders
- Urinary bladder dysfunction
- Gastrointestinal problems
- Autonomic dysfunction

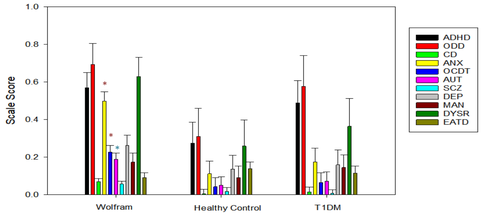
Background

- Existing literature suggests Wolfram Syndrome (WS) may have psychiatric manifestations.
- Our own research group has found evidence for increased internalizing symptoms, fatigue, and sleep problems in WS.

Methods

- This analysis focuses on information obtained during annual Wolfram Syndrome (WS) research clinics held at Washington University between the years of 2013 and 2017.
- Self- and parent-report questionnaires (including Checkmate Plus inventories) were used to screen for psychiatric symptoms and disorders.
- At each clinic visit, a child & adolescent psychiatrist (AMR) reviewed available questionnaires and interviewed affected individuals (and/or parents) to determine best-estimate lifetime psychiatric diagnoses. A total of 39 WS participants were interviewed at least once.
- Information regarding psychotropic medication use was also obtained during the interviews.
- Using 2014-2017 data, psychiatric symptom scores were created by averaging CASI-5 item responses in various categories. Covariate-adjusted scores were compared among WS (n=33), healthy control (HC, n=18), and type 1 diabetes mellitus (T1DM, n=15) participants.

Covariate-adjusted Mean Psychiatric Symptom Scores in Wolfram Syndrome (WS, n=33), Healthy Control (HC, n=18) Type 1 Diabetes Mellitus (T1DM, n=15), Participants



ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, CD = Conduct Disorder, ANX = Anxiety (includes symptoms from multiple types of anxiety disorders), OCDT = Obsessive-Compulsive Disorder and tics, AUT = Autism and Schizoid Personality, SCZ = Schizophrenia, DEP = Depression and Dysthymia, MAN = Mania, DYSR = emotional dysregulation/irritability, EATD = eating disorder symptoms. CASI-5 = Child and Adolescent Symptom Inventory 5. Scores are adjusted for sex, initial age, number of assessment time points.

Pairwise comparisons for subscales showing significant overall group differences:

*WS significantly different from HC (p<0.05): AUT

#WS significantly different from BOTH T1DM and HC (P<0.05): ANX, OCDT

Percent of WS participants with Each Best Estimate Lifetime Psychiatric Diagnosis (based on review of questionnaires plus clinical psychiatric interview)

Best Estimate Diagnoses	Children Age 6-12 yrs (n=12)	Adolescents Age 13-17 yrs (n=11)	Adults Age 18-30 yrs (n=16)	Total Age 6-30 yrs (n=39)
Any Neurodevelopmental or Disruptive Behavior Disorder	**50**	**27**	**19**	**31**
ADHD-full criteria	25	9	6	13
ADHD-unspecified	8	0	13	8
ADHD-any	33	9	19	21
Oppositional-Defiant Disorder	33	18	6	18
Conduct Disorder	0	9	0	3
Autism Spectrum Disorder	8	9	0	5
Tourette Syndrome	8	0	0	3
NDD-Unspecified	0	9	0	3
Any Anxiety Disorder	**92**	**82**	**63**	**77**
Generalized Anxiety Disorder	8	9	19	13
Social Anxiety Disorder	0	0	6	3
Separation Anxiety Disorder	8	19	0	8
Specific Phobia	8	9	6	8
Unspecified Anxiety Disorder	75	55	38	54
Any Obsessive-Compulsive Spectrum Disorder	**33**	**36**	**25**	**33**
Obsessive-Compulsive Disorder	0	0	13	5
Excoriation Disorder	33	27	13	23
Unspecified Obsessive-Compulsive Disorder	0	9	0	3
Any Mood Disorder	**25**	**27**	**38**	**31**
Major Depressive Disorder	0	0	19	8
Persistent Depressive Disorder/Dysthymia	0	9	0	3
Disruptive Mood Dysregulation Disorder	8	9	0	5
Unspecified Depressive Disorder	17	9	13	13
Unspecified Bipolar Disorder	0	0	6	3
Any Sleep Disorder	**17**	**27**	**38**	**31**
Hypersomnolence*	8	27	38	26
Sleep Apnea*	8	0	6	5
Restless Legs Syndrome/ Periodic Limb Movements of Sleep*	8	0	0	3
Unspecified Sleep Disorder	0	0	6	3
Hallucinations	**50**	**27**	**38**	**38**
Unspecified Psychotic Disorder	**8**	**0**	**0**	**3**
Unspecified Eating Disorder	**8**	**0**	**0**	**3**
Any Trauma and Stressor Related Disorder	**8**	**9**	**19**	**13**

*Sleep apnea and restless legs/periodic limb movements diagnoses were given based on symptoms and past sleep study results reported during psychiatric interviews. Since a minority of patients/parents reported past sleep study results, these percentages are likely to be underestimates. Some hypersomnolence or unspecified sleep disorder cases might be explained by a more specific sleep disorder if more information was available. A separate analysis including ambulatory sleep study data has found high rates of sleep apnea (Licis et al., 2019).
Ages are based on the most recent clinic visit.

Psychotropic Medications taken by WS participants

Medication	Reported Dose Range (total daily)	Target Symptoms (reported during interview)	Adverse Effects (reported during interview)	Effectiveness Rating
citalopram	10-40 mg	anxiety, depression	?	+++
fluoxetine	40-60 mg	anxiety, OCD, depression	possible heat intolerance and blood pressure changes	++
sertraline	25-150 mg	anxiety, OCD, restricted-repetitive behaviors, depression, low social motivation	euphoric mood, gastrointestinal symptoms (diarrhea, nausea, vomiting)	+/-
venlafaxine	37.5-75 mg	anxiety	gastrointestinal symptoms	+/--
duloxetine	90-120 mg	anxiety, depression, neuropathic pain	?	++
amitriptyline		insomnia	chest pain	---
bupropion	150-400 mg	depression, anxiety	mood swings, nighttime awaking with bad dreams, agitation, and panic symptoms	+/-
mirtazapine	unknown	insomnia	Increased appetite, morning sedation, dizziness	---
trazodone	unknown	insomnia	muscle aches, bad dreams, restless sleep	---
buspirone	unknown	anxiety	?	+/-
alprazolam	unknown, as needed	anxiety, panic	Sedation, "felt like a zombie"	+
lorazepam	unknown	anxiety, panic, insomnia	?	+
clonazepam	unknown	insomnia	?	+/-
prazosin	unknown	insomnia	morning sedation, dizziness	---
guanfacine	4 mg	ADHD, help lower blood pressure	?	+
hydroxyzine	25-100 mg	anxiety	?	+
diphenhydramine	50-100 mg	insomnia	?	+
melatonin	3-20 mg	insomnia	?	+
modafinil	unknown	daytime sleepiness	?	++
armodafinil	400 mg	daytime sleepiness	?	++
lisdexamfetamine	20-70 mg	ADHD, daytime sleepiness	?	++
dexmethylphenidate	10 mg	daytime sleepiness	?	++
atomoxetine	100 mg	ADHD	?	+
lamotrigine	unknown	Depression, mood instability	?	++
levetiracetam	2000-3000 mg	seizures	?	+/-
phenytoin	200 mg	seizures	?	+/-
gabapentin	600 mg	neuropathic pain	sedation	+/-
lithium	unknown	mood instability	?	+/-
aripiprazole	unknown	mood instability, aggression	?	+/-
risperidone	0.25-1 mg	OCD, anxiety, mood instability, irritability, aggression	sedation, possible heat intolerance and blood pressure changes, increased appetite, depression	+

Explanation of Effectiveness Rating:

+++ = More than one WFS patient reported clear benefit, few or no reports of non-response or side effects.
++ = At least one WFS patient reported clear benefit, few or no reports of non-response or side effects.
+ = At least one WFS patient reported some benefit, few or no reports of substantial side effects.
+/- = Response unclear, or equal number of patients reported good vs. poor response.
-- = Non-response or intolerable side effects reported more often than good response.
--- = No clear benefits reported and substantial adverse side effects were reported.

Response to SSRIs

- 33% (n=13) reported current or past treatment with a selective serotonin re-uptake inhibitor (SSRI). This included sertraline (n=9), fluoxetine (n=3), and citalopram (n=6). Five had taken both sertraline and another SSRI.
- 23% (n=9) were taking an SSRI at their most recent clinic visit and reported benefits for mood and/or anxiety symptoms.
- 78% of sertraline trials were reportedly stopped due to ineffectiveness or side effects, but only 22% of fluoxetine or citalopram trials had been discontinued as of the most recent clinic visit ($\chi2=5.56$, p=0.018), suggesting sertraline may be less helpful than other SSRIs in WS.
- Animal studies suggest that most SSRIs have sigma1 receptor agonist activity (which may ameliorate ER stress), but sertraline may instead be a sigma1 antagonist. This is a possible explanation for differences in treatment response depending on the specific SSRI that is used.
- Based on the above, SSRIs with sigma1 agonist effects (fluvoxamine, fluoxetine, citalopram, escitalopram) may be the SSRIs of choice in WS, but further study is needed to confirm this.

Disclosures:

- Dr. Reiersen has received travel support from Child & Adolescent Psychiatric Department, Region Zealand (a hospital in Denmark) to attend another scientific meeting.
- All other authors have no real or potential conflicts of interest to disclose.

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Conclusions:

Psychiatric disorders are common in WS, and anxiety is particularly prevalent. Although any chronic, progressive disease might increase anxiety, it may also be that a dysregulated ER stress response resulting from WFS1 gene dysfunction contributes to psychiatric symptoms in WS. Further studies correlating measures of brain structure and function with psychiatric symptoms may clarify underlying mechanisms. Future treatment studies are needed to determine the most appropriate interventions. Since altered ER stress response has recently been implicated as a possible mechanism of some psychiatric conditions, further study of WS may also have relevance to psychiatric disorders more generally.

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