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PSYCHOTROPIC MEDICATION USAGE IN INDIVIDUALS WITH FETAL ALCOHOL SPECTRUM DISORDER (FASD) AND PSYCHIATRIC CO-MORBIDITIES IN CANADA

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ABSTRACT

Background and objective

Individuals with Fetal Alcohol Spectrum Disorder (FASD) tend to be prescribed a high number of psychotropic medications to treat high rates of comorbid psychiatric disorders. A lack of guidance regarding best practices for prescribing psychotropic medications to individuals with FASD probably accounts for this reliance on polypharmacy. The objective of this study is to describe the types of medications prescribed to individuals with prenatal alcohol exposure, comparing rates between individuals diagnosed with FASD and individuals without FASD as well as how medications are prescribed based on age, sex, and comorbid psychiatric disorders.

Material and methods

Data were drawn from Canada's national FASD database. This database includes information collected during an FASD assessment related to diagnostic outcomes, secondary challenges, and medical and mental health information. Descriptive statistics were calculated for four diagnostic groups (FASD with sentinel facial features [FASD + SFF], FASD without sentinel facial features [FASD - SFF], at risk for FASD ["at risk"], and no FASD). Group demographics were compared using Chi-Square, Fisher's Exact Test, and ANOVA, as appropriate. Differences in the proportion of individuals between these four diagnostic groups were calculated using each of the following six classes of psychotropic medications—antipsychotics, antidepressants/anxiolytic, anticonvulsants/mood stabilizers, stimulants, melatonin, and others—using ANOVA. Considering just the individuals with FASD by combining the FASD + SFF and FASD - SFF groups, independent sample tests were used to compare differences in the proportion of males and females prescribed different medications. Chi-Square and Fisher's Exact Test were used to compare the proportion of individuals using psychotropic medications, according to category, within the FASD group based on the presence or absence of 13 comorbid psychiatric disorders.

Results

The overall sample included 2349 participants (mean value = 18.1 years, SD = 10.3). The sample included 1453 participants with an FASD diagnosis (n = 218, FASD + SFF, mean = 23.7 years, SD = 15.8, and n =

1235, FASD - SFF, mean = 19.5 years, SD = 10.0 years) and 896 participants who were assessed but did not receive an FASD diagnosis (n = 653, no FASD, mean = 16.1 years and n = 261, "at risk" for FASD, mean = 12.2 years). The FASD groups had a significantly higher rates of anxiety disorders, depressive disorders, and the presence of at least one comorbid psychiatric disorder compared to the no FASD and the "at risk" groups. Both FASD groups had a higher proportion of individuals taking antipsychotic and antidepressant/anxiolytic medications compared to the no FASD and "at risk" groups. Females with FASD were more often prescribed antidepressants/anxiolytics compared to males with FASD, while males with FASD were more often prescribed stimulants than females with FASD. The prevalence of antidepressants/anxiolytics, stimulants, and melatonin use by individuals with FASD differed across the lifespan. The prevalence of the prescription of six medication categories was found to differ according to psychiatric disorder.

Conclusion

Compared to individuals assessed as not fulfilling criteria for FASD, those with FASD had higher rates of psychiatric disorders and were prescribed significantly more antidepressants/anxiolytics and antipsychotics. The class and rate of prescriptions may support efforts in devising treatment guidelines for a complex disorder with known high comorbidity such as FASD.

INTRODUCTION

Fetal Alcohol Spectrum Disorder (FASD) is a diagnostic term used to describe the lifelong impact on the brain and body of individuals who experienced prenatal alcohol exposure (PAE).[1,2] Prevalence of FASD in Canada is estimated to be between 1% and 4%, but this is probably an underestimation.[3] Individuals with FASD experience various functional impairments, including cognitive deficits, reduced impulse control, learning disabilities, attentional problems, and motor issues as well as a host of physical and psychiatric disorders.[4,5]

The Canadian diagnostic guidelines for FASD[1] describe two possible FASD diagnoses: FASD with sentinel facial features (FASD + SFF) or FASD without sentinel facial features (FASD - SFF). A diagnosis of FASD + SFF is made if an individual with confirmed PAE has upper lip thinness and a smoothed philtrum ridge that meet the agreed threshold of the Washington Lip-Philtrum Guide, having a score of 4 or 5, and the mean palpebral fissure score is >2 standard deviations below the mean value, along with impairment in at least three of the 10 brain domains known to be impaired by PAE. A diagnosis of FASD - SFF is made if <3 or no sentinel facial features are present when PAE is confirmed, and ≥3 brain domains are impaired. The Canadian diagnostic guidelines also outline the designation of "at risk" for FASD.[1] The "at risk" designation is given if enough information is not available to conclude an FASD diagnosis (e.g., when an assessment cannot be conducted in full, or an individual is too young to assess all brain domains), yet there is confirmed PAE and evidence of brain domain impairment. Individuals designated as "at risk" are recommended a follow-up FASD assessment in the future. When an FASD assessment is completed in full, but diagnostic criteria for FASD are not met, the individual is deemed to not have FASD ("no FASD").

Psychiatric disorders are commonly experienced by individuals with FASD,[6,7] with some researchers determining that the prevalence rate is as high as 90%.[8] Attention Deficit Hyperactivity Disorder (ADHD) affects 50–90% of individuals with FASD.[4,9] Disruptive behaviors, disorders of mood, anxiety, substance misuse, impulse control, and conduct disorder, as well as educational problems, are also seen at increased rates in this population.[4,6,9–11] The higher prevalence of psychiatric disorders in individuals with FASD has led some researchers to state that PAE should be

considered as a potential contributing factor to the development of psychiatric disorders in childhood, including ADHD and developmental coordination disorder.[12–14] This is a particularly important consideration, given that the early onset of mental health issues can be a risk factor for chronic and future psychiatric disorders.[12]

Effective treatment for different conditions associated with FASD, such as psychiatric disorders, is a challenge that necessitates a biopsychosocial approach. Understanding the complexities and needs of individuals with FASD allow for the identification of the most relevant interventions and supports. These interventions are imperative, given the well-documented increased risk of suicide[15] and the disproportionate number of individuals with FASD who have been incarcerated, have experienced employment challenges, or struggled in the education system.[10,16] Researchers have provided initial validation of the psychosocial approach to treat conditions associated with FASD, focusing on lifestyle and behavioral interventions to improve outcomes.[17–19] Determining the effectiveness of pharmacotherapy in treating psychiatric disorders in individuals with FASD is still developing.

The current psychopharmacological approach for individuals with FASD has relied on clinical judgment and pre-existing guidelines for the treatment of comorbid psychiatric disorders in other populations with neurodevelopmental disorders.[17] As Mela[20] notes, off-label prescribing of psychotropic medications for individuals with PAE/FASD is a norm; however, little is known about the efficacy and potential adverse outcomes of the use of psychotropic medication in this population,[20] potentially because of the lack of understanding of how the mechanism of psychotropic medication is affected by the structural and functional brain differences associated with PAE/FASD. Research on the use of psychotropic medications for people with Autism Spectrum Disorder (ASD) has shown that a key component of providing appropriate and effective prescriptions is treatment provider's knowledge of ASD, and yet general practitioners often do not feel comfortable treating these individuals for psychiatric disorders.[21] Further, despite there being guidelines for prescribing psychotropic medications for individuals with other intellectual and/or neurodevelopmental disorders, including ASD, they often go without follow-up, leading to polypharmacy,[22] which increases the risk of adverse effects of psychotropic medications.[23] FASD is a lifelong disorder, yet pediatricians report the most comprehensive training related to FASD, and only 55% of pediatricians report this level of training.[24] This lack of training and knowledge may have an impact on the use of psychotropic medications for individuals with FASD and psychiatric disorder(s).

Researchers have reported that the most common medications prescribed for individuals with FASD are stimulants, atypical antipsychotics, mood stabilizers, and antidepressants/anxiolytics.[20] Less is known about whether the use of these medications is higher in individuals with FASD compared to other populations.[20] The use of stimulants by individuals with FASD is known to be effective for ADHD symptoms of hyperactivity and impulsivity, but less so for inattentiveness.[25,26] Antipsychotics tend to reduce externalizing behavior, behavioral disruption, conduct disorders, and aggression in individuals with FASD.[27,28] Mood stabilisers are effective for mood dysregulation, aggression, and reduction in the risk of developing mania,[29] and antidepressants and anxiolytics are also noted to be effective in children with FASD.[30] Finding the right indication for psychotropic medications should contribute to their effectiveness, improve the function of the individual taking the medication, and reduce both over-prescription and adverse effects in individuals with FASD.[29] This led a group of experts to develop a medication algorithm as a guideline to manage clusters of symptoms associated with FASD.[26] However, little is still known about prescription patterns for individuals with FASD who have comorbid psychiatric disorders. Despite the evidence that psychotropic medications are effective in treating psychiatric conditions associated with FASD, additional research in this area is necessary to understand the

benefits and risks of using psychotropic medication in this population. Additional research is required due to the necessity of treating comorbid psychiatric disorders in individuals with FASD,[9] limited guidance on how to prescribe psychotropic medication for individuals with FASD,[31] and the high rate of polypharmacy in this population.[32]

The purpose of the current study was to describe (1) the types of psychotropic medications prescribed to individuals with PAE/FASD and at what frequency, based on diagnostic outcome, and (2) which medications are prescribed to individuals who receive an FASD diagnosis based on age, sex, and presence or absence of a comorbid psychiatric disorder. Data were collected from individuals who underwent an FASD assessment and had confirmed PAE.[33] Individuals with PAE who did not receive an FASD diagnosis were included in the database to capture information on the impairments associated with PAE even when diagnostic criteria for FASD were not met, effectively acting as a control group for individuals with confirmed PAE and an FASD diagnosis. This study begins to address the knowledge gap in the use of psychotropic medication for individuals with FASD as well as how the prescription of psychotropic medication is influenced by age, sex, and comorbid psychiatric disorders. Our results contribute to the evidence-base required to support the prescription of appropriate psychotropic medications for individuals with FASD.

METHODS

This study involved a secondary analysis of data from the Canadian National FASD Database (the database), which includes anonymized, in-depth, patient-level information on individuals presenting for an FASD assessment.[33] Ethical approval for using this data was granted by the Research Ethics Board at the University of Saskatchewan (REB# Bio-17-305). Data were provided by FASD diagnostic clinics from seven Canadian provinces and territories, and included diagnostic criteria based upon the Canadian diagnostic guidelines for FASD as well as additional information on demographics, mental and physical health, behavioral, and medications.[33]

The database was originally developed based on the 2005 Canadian FASD diagnostic guidelines.[34] Following the creation and implementation of the 2015 Canadian FASD diagnostic guidelines, the database was revised to reflect the new diagnostic criteria. To ensure that records from the database included in this study were representative of contemporary diagnostic criteria, inclusion criteria for records in the data extraction were (1) database records from 2016 to the time of data extraction in September 2020, and (2) diagnostic assessment outcome with respect to an FASD diagnosis (including participants with no FASD diagnosis and those given the designation of "at risk"). As per ethical approval, a waiver for consent was granted due to the secondary use of anonymized data.

Data collection methods and relevant variables

Variables analyzed in this study are listed in Table 1. Suicidality was included as a psychiatric disorder. Although suicidality (defined in the database as suicidal ideation and/or attempts) is not a psychiatric disorder by definition in the Diagnostic and Statistical Manual for Mental Disorders-5 (DSM-5),[35] it is associated broadly with psychiatric disorders[36] and has a high prevalence in this population.[15,37]

Ten brain domains are assessed during the FASD diagnostic process. Brain domain impairment is defined as "significantly impaired" (standardized score on the relevant clinic measure for each brain domain of ≥2 SD below the mean value) or "not impaired" (any score <2 SD below the mean value).[1] In the database, the presence of each psychiatric disorder is coded as "Yes" (present) or "No" (absent). The presence or absence of a depressive and/or anxiety disorder is determined by clinicians formally obtaining this information as per the diagnostic guidelines.[1] Information on the presence or absence of other psychiatric disorders may come from self-report, a formal diagnosis formed during the multidisciplinary diagnostic assessment, or recent psychological assessments, such as those

TABLE 1 Study Variables.

Variables of Interest
Demographics
Age
Sex
Full scale IQ
Brain domain impairment
Motor skills
Neuroanatomy
Cognition
Language
Academic achievement
Memory
Attention
Executive functioning
Affect regulation
Adaptive behavior
Psychiatric disorders
Attention Deficit/hyperactivity disorder
Attachment disorder
Tourette syndrome
Anxiety disorder
Autism spectrum disorder
Bipolar disorder
Conduct disorder
Depressive disorder
Obsessive-compulsive disorder
Personality disorder
Post-traumatic stress disorder
Schizophrenia
Substance use disorder
Suicidality
Psychotropic medications
Antipsychotics
Antidepressants
Anticonvulsants (mood stabilizers)
Stimulants
Melatonin
Other

conducted by psychologists, psychiatrists, or developmental pediatricians. The current *use* of psychotropic medications is indicated, and the names of medications are provided.

Data Analysis

Descriptive statistics were generated to characterize the study sample and involve the calculation of frequencies (%) for categorical variables and mean and standard deviation for continuous variables. Comparisons across four diagnostic groups (i.e., FASD + SFF, FASD - SFF, "at risk," and no FASD) were performed using Pearson's Chi-square or Fisher's Exact Test (for categorical variables) and ANOVA (for continuous variables). Medications were categorized into one of the following six groups: antipsychotics (e.g., risperidone, quetiapine, etc.), antidepressants/anxiolytics (e.g., fluoxetine, venlafaxine, etc), anticonvulsants (often prescribed as mood stabilizers; e.g., lamotrigine), stimulants (e.g., methylphenidate, lisdexamfetamine, etc.), melatonin, and others (e.g., omega-3, choline, glutamine, minocycline, and buspirone), and the proportion of individuals currently using these medications was compared between the four diagnostic groups.

Data from both FASD + SFF and FASD - SFF groups were combined to create a single FASD group for the remaining analyses. The proportion of individuals currently using the six categories of psychotropic medications was compared according to sex, age, and between those with and without the presence of each of the psychiatric disorders of interest using *post hoc* comparisons. Bonferroni corrections were applied wherever appropriate to assess significant associations while accounting for multiple comparisons. Statistical analyses were conducted using SPSS v26. Statistical tests were considered significant at $p < 0.05$ (two-tailed comparison $\alpha = 0.05$).

The sample size for each analysis varied due to missing data. To avoid decreasing the overall sample size, cases with missing data were still included in this study. Therefore, the denominator used when calculating rates and the sample size used in each analysis varied based upon the amount of data available. Further, if a psychiatric disorder was not self-reported or assessed during the multidisciplinary FASD assessment, it can be indicated in the database as "not assessed." Because a disorder was not assessed, and without evidence that the disorder had been diagnosed prior to the FASD assessment, neither the presence nor absence of the disorder can

be accurately concluded. Therefore, cases where a disorder was indicated to not have been assessed were excluded. Sample size for each variable was noted in tables and/or table notes, where appropriate.

RESULTS

Sample characteristics

At the time of data extraction (September 2020), the database included n = 2378 cases. Once records with missing information on confirmed PAE, unconfirmed PAE, and missing diagnostic outcomes were excluded, n = 2349 cases were included in analyses. Sample characteristics are given in Table 2. The sample included 218 cases with FASD + SFF (9.3%), 1235 cases with FASD - SFF (52.6%), 261 "at risk" cases (11.1%), and 635 cases with no FASD diagnosis (27.0%). The sample included children aged <12 years (n = 577, 24.6%), adolescents (12–17 years; n = 810, 34.5%), transition-aged youth (18–24 years; n = 572, 24.4%), and adults aged ≥25 years (n = 390, 16.6%), with the mean age of the total sample being 18.1 years (SD = 10.3).

Age significantly differed according to diagnostic group ($F(3, 2343) = 71.87$, $p < 0.001$). Individuals in the FASD + SFF group (M = 23.7, SD = 15.8) were significantly older than those in the FASD - SFF group (M = 19.5, SD = 10.0, $p < 0.001$), the "at risk" group (M = 12.2, SD = 5.1, $p < 0.001$), and the no FASD group (M = 16.1, SD = 8.6, $p < 0.001$). Individuals in the FASD - SFF group were also significantly older than those "at risk" and with no FASD diagnosis (all p-values <0.001). Finally, those with no FASD diagnosis were significantly older than those in the "at risk" group ($p < 0.001$). Over half of the total sample was male (n = 1351, 57.5%) but there was no significant difference in sex across diagnostic groups, $\chi^2(3, n = 2345) = 5.30$, $p = 0.15$).

One-third (n = 659, 34.0%) of the samples had a full-scale IQ score of less than 70 (i.e., 2 SD below the population mean value, a criterion commonly used when considering a diagnosis of intellectual disability).[38] Cases diagnosed with FASD + SFF/FASD - SFF (n = 600) accounted for 91% of lower IQ cases. IQ < 70 was also more prevalent in the FASD + SFF group (n = 108, 58.1%) than in the FASD - SFF group (n = 492, 46.0%) ($\chi^2(6, n = 1940) = 467.17$, $p < 0.001$). Across the sample, the most commonly impaired neurodevelopmental domains were attention (61.1%), academic achievement (58.9%), executive functioning (58.3%), adaptive behavior (54.5%), and cognition (50.0%). High rate of total brain domain impairment was apparent across the sample (M = 3.9, SD = 2.4), and the rate of impairment differed between the four groups ($F(3, 2345) = 599.64$, $p < 0.001$) (Table 2). The FASD + SFF group (M = 5.5, SD = 2.0) had significantly higher total brain domain impairments than the FASD - SFF group (M = 5.1, SD = 1.6, $p < 0.01$), the "at risk" group (M = 2.0, SD = 1.6; $p < 0.001$), and the no FASD group (M = 1.9, SD = 2.0; $p < 0.001$). The FASD - SFF group had significantly higher total brain domain impairments than the "at risk" group ($p < 0.001$) and the no FASD diagnosis group ($p < 0.001$).

Comorbid psychiatric disorder(s) (n = 927) were observed in 50% of samples, and depressive disorders were most prevalent (n = 416, 38.9%). Significant differences across diagnostic groups were observed for rates of anxiety disorders ($\chi^2(3, n = 1199) = 24.46$, $p < 0.001$), conduct disorder ($\chi^2(3, n = 879) = 25.85$, $p < 0.001$), depressive disorders ($\chi^2(3, n = 1070) = 48.63$, $p < 0.001$), post-traumatic stress disorder (PTSD; $\chi^2(3, n = 624) = 10.69$, $p < 0.05$), schizophrenia ($\chi^2(3, n = 520) = 12.08$, $p < 0.01$), substance use ($\chi^2(3, n = 937) = 23.67$, $p < 0.001$), and suicidality ($\chi^2(3, n = 997) = 21.99$, $p < 0.001$). Prevalence of these mental health conditions was not different between FASD + SFF and FASD - SFF groups but was significantly higher in these two groups compared to the "at risk" and no FASD diagnosis groups (all p-values <0.01) (Table 2).

Use of Psychotropic Medication According to Group

Prescription medication according to diagnostic groups is presented in Table 3. Chi-square analyses showed that there were significant differences

TABLE 2 Sample Characteristics according to Group.

Variables	Overall Sample (n = 2349) n (%)	FASD + SFF (n = 218) n (%)	FASD - SFF (n = 1235) n (%)	At Risk (n = 261) n (%)	No FASD (n = 635) n (%)
Age in years (M, SD) (n = 2347)	18.1 (10.3)	23.7 (15.8)[a]	19.5 (10.0)[b]	12.2 (5.1)[c]	16.1 (8.6)[d]
Age Group (n = 2349)					
<12 years (children)	577 (24.6%)	60 (27.5%)[a]	204 (16.5%)[b]	124 (47.5%)[c]	189 (29.8%)[a]
12–17 years (adolescents)	810 (34.5%)	33 (15.1%)[a]	430 (34.8%)[b]	110 (42.1%)[b]	237 (37.3%)[b]
18–24 years (transition-aged youth)	572 (24.4%)	45 (20.6%)[a, b]	357 (28.9%)[b]	23 (8.8%)[c]	147 (23.1%)[a]
≥25 years (adults)	390 (16.6%)	80 (36.7%)[a]	244 (19.8%)[b]	4 (1.5%)[c]	62 (9.8%)[d]
Sex (n = 2345)					
Male	1351 (57.6%)	132 (60.6%)[a]	726 (58.9%)[a]	151 (58.3%)[a]	342 (53.9%)[a]
Female	994 (42.4%)	86 (39.4%)[a]	507 (41.1%)[a]	108 (41.7%)[a]	293 (46.1%)[a]
IQ (n = 1940)					
<70	659 (34.0%)	108 (58.1%)[a]	492 (46.0%)[a]	15 (8.1%)[b]	44 (8.8%)[b]
70–85	793 (40.9%)	60 (32.3%)[a]	448 (41.9%)[a]	81 (43.8%)[a]	204 (40.8%)[a]
>85	488 (25.2%)	18 (9.7%)[a]	129 (12.1%)[a]	89 (48.1%)[b]	252 (50.4%)[b]
Impaired Neurodevelopmental Domains					
Motor skills (n = 2102)	462 (22.0%)	75 (39.5%)[a]	294 (27.3%)[b]	24 (10.2%)[c]	69 (11.5%)[c]
Neuroanatomy (n = 1969)	180 (9.1%)	51 (28.0%)[a]	78 (7.7%)[b,c]	23 (10.4%)[c]	28 (5.1%)[b]
Cognition (n = 2222)	1111 (50.0%)	154 (74.8%)[a]	821 (69.2%)[a]	43 (18.5%)[b]	93 (15.6%)[b]
Language (n = 2183)	841 (38.5%)	107 (54.6%)[a]	565 (48.8%)[a]	52 (22.7%)[b]	117 (19.5%)[b]
Academic (n = 2106)	1240 (58.9%)	149 (75.3%)[a]	874 (74.3%)[a]	80 (40.4%)[b]	137 (25.7%)[c]
Memory (n = 2101)	839 (39.9%)	119 (62.0%)[a]	610 (53.1%)[a]	28 (14.4%)[b]	82 (14.5%)[b]
Attention (n = 2162)	1321 (61.1%)	139 (70.6%)[a]	824 (71.0%)[a]	119 (52.9%)[b]	239 (41.2%)[c]
Executive (n = 2126)	1239 (58.3%)	162 (79.0%)[a]	857 (73.1%)[a]	53 (26.9%)[b]	167 (30.3%)[b]
Affect regulation (n = 2073)	765 (36.9%)	103 (55.4%)[a]	493 (44.8%)[b]	43 (20.0%)[c]	126 (22.0%)[c]
Adaptive (n = 2,216)	1208 (54.5%)	147 (72.8%)[a]	851 (72.0%)[a]	53 (23.3%)[b]	157 (26.0%)[b]
Total number of impaired brain domains (M, SD) (n = 2349)	3.9 (2.4)	5.5 (2.0)[a]	5.1 (1.6)[b]	2.0 (1.6)[c]	1.9 (2.0)[c]
Psychiatric Disorders					
ADHD (n = 2160)	1224 (56.7%)	109 (54.0%)[a]	730 (64.6%)[b]	113 (46.3%)[a]	272 (46.6%)[a]
Attachment (n = 1271)	146 (11.5%)	14 (10.4%)[a]	83 (12.4%)[a]	18 (14.0%)[a]	31 (9.1%)[a]
Tourette (n = 858)	15 (1.7%)	1 (1.3%)[a]	8 (1.9%)[a]	0 (0.0%)[a]	6 (2.3%)[a]
Anxiety disorder (n = 1199)	399 (33.3%)	60 (41.7%)[a]	248 (36.7%)[a]	26 (19.7%)[b]	65 (26.3%)[b]
Autism (n = 665)	48 (7.2%)	7 (9.7%)[a]	21 (6.5%)[a]	5 (5.6%)[a]	15 (8.3%)[a]
Bipolar disorder (n = 548)	25 (4.6%)	5 (8.8%)[a]	12 (4.4%)[a]	0 (0.0%)[a]	8 (5.7%)[a]
Conduct disorder (n = 879)	148 (16.8%)	19 (17.8%)[a,b]	106 (21.7%)[b]	4 (3.9%)[c]	19 (10.4%)[a,c]
Depressive disorder (n = 1070)	416 (38.9%)	71 (53.8%)[a]	267 (43.3%)[a]	21 (18.9%)[b]	57 (27.0%)[b]

(continues)

TABLE 2 Continued

Variables	Overall Sample (n = 2349) n (%)	FASD + SFF (n = 218) n (%)	FASD - SFF (n = 1235) n (%)	At Risk (n = 261) n (%)	No FASD (n = 635) n (%)
OCD (n = 714)	34 (4.8%)	5 (6.1%)[a]	20 (5.1%)[a]	3 (3.3%)[a]	6 (3.9%)[a]
Personality disorder (n = 565)	43 (7.6%)	6 (10.7%)[a]	25 (8.5%)[a]	2 (2.6%)[a]	10 (7.2%)[a]
PTSD (n = 624)	146 (23.4%)	20 (30.8%)[a]	70 (22.7%)[a,b]	10 (11.6%)[b]	46 (28.0%)[a]
Schizophrenia (n = 520)	19 (3.7%)	1 (2.0%)[a,b]	17 (6.4%)[b]	1 (1.3%)[a,b]	0 (0.0%)[a]
Substance abuse disorder (n = 937)	253 (27.0%)	33 (29.2%)[a]	170 (31.1%)[a]	8 (8.2%)[b]	42 (23.5%)[a]
Suicidality (n = 997)	212 (21.3%)	31 (26.1%)[a]	128 (23.7%)[a]	5 (4.5%)[b]	48 (21.0%)[a]
Having at least one of the 14 mental health conditions mentioned above (n = 2349)	1605 (68.3%)	160 (73.4%)[a]	958 (77.6%)[a]	136 (52.1%)[b]	351 (55.3%)[b]

ADHD: Attention Deficit/Hyperactivity Disorder; FASD: Fetal Alcohol Spectrum Disorder; SFF: sentinel facial features; IQ: intelligence quotient; M: mean; SD: standard deviation.
Samples varied due to missing data; Percentage (%) values were calculated based on valid denominator for each variable. Overall sample: n = 520–2349; FASD + SFF: n = 51–216; FASD – SFF: n = 266–1235; "at risk": n = 75–261; no FASD diagnosis: n = 128–635.
Each superscript letter denotes a subset of diagnostic group whose column proportions do or do not differ significantly from each other at 0.05 level. Same superscript letters across columns indicate no significant difference, while different superscript letters indicate significant differences.
Note: p-values reported in the text are the Bonferroni corrected p-values that have been adjusted for the number of comparisons made.

between groups in the prevalence of antipsychotics ($\chi^2(3, n = 2349) = 10.80$, $p < 0.05$) and antidepressant/anxiolytic medications ($\chi^2(3, n = 2349) = 30.19$, $p < 0.001$). Prescription of antipsychotic medications was significantly more prevalent in the FASD -SFF group (12.1%) than in the "at risk" group (5.7%, $\chi^2(1, n = 1496) = 8.99$, $p < 0.01$). Antidepressant/anxiolytic medications were prescribed more often to patients with FASD + SFF (13.8%) compared to the "at risk" group (4.6%; $\chi^2(1, n = 479) = 12.47$, $p < 0.001$) and the no FASD group (5.5%, $\chi^2(1, n = 853) = 15.69$, $p < 0.001$). Antidepressant/anxiolytic medications were prescribed more often to the FASD - SFF group (11.6%) compared to the "at risk" group ($\chi^2(1, n = 1235) = 11.31$ $p < 0.001$).1) and the no FASD group ($\chi^2(1, n = 1870) = 17.92$, $p < 0.001$).

Use of Psychotropic Medication According to Sex

As shown in Table 4, there were significant sex differences in the prescription of antidepressant/anxiolytic and stimulant medications. Prevalence of antidepressant/anxiolytic medication prescriptions was higher among females with FASD (15.0%) than in males with FASD (9.8%; $\chi^2(1, n = 1451) = 9.09$, $p < 0.01$). In contrast, prevalence of stimulant medications was significantly higher among males (24.1%) compared to females with FASD (16.9%; $\chi^2(1, n = 1451) = 11.09$, $p = 0.001$). There were no significant differences between male and female participants in the prescriptions of antipsychotic, anticonvulsant, melatonin, and other medications (all p-values <0.05).

Use of Psychotropic Medication According to Age

Among the six groups of medications prescribed to individuals with FASD, prescription rates of antidepressant/anxiolytic medication ($\chi^2(3, n = 1453) = 61.49$, $p < 0.001$), stimulant medication ($\chi^2(3, n = 1453) = 56.03$, $p < 0.001$), and melatonin ($\chi^2(3, n = 1181) = 32.28$, $p < 0.001$) significantly differed according to age groups (Table 5). Prescription of

TABLE 3 Prevelence of Psycotropic Medication Prescription according to Diagnostic Groups.

Medication Group FASD + SFFn	(%)	FASD - SFF n (%)	At Risk n (%)	No FASD n (%)
Antipsychotic medications (n = 2349)	26 (11.9%)[a,b]	150 (12.1%)[b]	15 (5.7%)[a]	60 (9.4%)[a,b]
Antidepressant/anxiolytic medications (n = 2349)	30 (13.8%)[a]	143 (11.6%)[a]	12 (4.6%)[b]	35 (5.5%)[b]
Anticonvulsant medications (n = 2349)	2 (0.9%)[a]	15 (1.2%)[a]	2 (0.8%)[a]	7 (1.1%)[a]
Stimulant medications (n = 2349)	34 (15.6%)[a]	273 (22.1%)[a]	43 (16.5%)[a]	149 (23.5%)[a]
Melatonin (n = 1935)	17 (9.7%)[a]	147 (14.6%)[a]	32 (14.5%)[a]	64 (12.0%)[a]
Other medications (omega 3, choline, glutamine, minocycline, buspirone) (n = 1947)	4 (2.2%)[a]	9 (0.9%)[a]	1 (0.4%)[a]	4 (0.7%)[a]

FASD: Fetal Alcohol Spectrum Disorder; SFF: sentinel facial features.
Each superscript letter denotes a subset of the diagnostic group whose column proportions do or do not differ significantly from each other at 0.05 level. Same superscript letters across columns indicate no significant difference, while different superscript letters indicate significant differences.
Note: p-values reported in the text are the Bonferroni corrected p-values that have been adjusted for the number of comparisons made.

TABLE 4 Prevalence of Medication Prescriptions According to sex among Individuals with FASD.

Medication Group	Male n (%)	Female n (%)	*p*
Antipsychotic medications (n = 1451)	107 (12.5%)	69 (11.6%)	0.63
Antidepressant/anxiolytic medications (n = 1451)	84 (9.8%)	89 (15.0%)	0.003[a]
Anticonvulsant medications (n = 1451)	11 (1.3%)	6 (1.0%)	0.64
Stimulant medications (n = 1451)	207 (24.1%)	100 (16.9%)	0.001[b]
Melatonin (n = 1181)	104 (15.0%)	60 (12.3%)	0.18
Other medications (omega 3, choline, glutamine, minocycline, buspirone) (n = 1184)	8 (1.2%)	5 (1.0%)	0.83

[a]$p < 0.01$; [b]$p = 0.001$.

antidepressant/anxiolytic medications appeared to increase with age, with the lowest use among children aged <12 years (1.9%) and highest among adults (21.0%). Except for transition-aged youth and adults, in whose case prevalence of antidepressant/anxiolytic medications prescribed did not differ significantly (15.4% vs. 21.0%, $p = 0.30$), all other age group comparisons were significantly different (all p-values ≤0.01; Table 5). Prevalence of stimulant medications was significantly higher among children aged <12 years (24.6%; $\chi^2(1, n = 588) = 32.07$, $p < 0.001$), adolescents (29.4%; $\chi^2(1, n = 787) = 54.94$, $p < 0.001$), and transition-aged youth (20.1%; $\chi^2(1, n = 726) = 22.24$, $p < 0.001$) than in adults (7.7%). Prescription of stimulant medication was also significantly higher in adolescents than in transition-aged youth ($p = 0.01$). Following the same pattern of prescription with stimulant medications, prevalence of melatonin prescription was highest in case of adolescents (20.0%) and lowest in case of adults (3.8%). Prescription of melatonin was also significantly higher among adolescents ($\chi^2(1, n = 630) = 32.06$, $p < 0.001$), children aged <12 years (14.2%, $\chi^2(1, n = 460) = 15.29$, $p < 0.001$), and transition-aged youth (13.5%; $\chi^2(1, n = 561) = 14.92$, $p < 0.001$) compared to adults (3.8%).

TABLE 5 Prevalence of Psychotropic Medication Prescriptions According to Age Groups among Individuals with FASD.

Medication Group	<12 years (Children) n (%)	12–17 years (Adolescents) n (%)	18–24 years (Transition-Aged Youth) n (%)	≥25 years (Adults) n (%)
Antipsychotic medications (n = 1453)	26 (9.8%)[a]	69 (14.9%)[a]	53 (13.2%)[a]	28 (8.6%)[a]
Antidepressant/anxiolytic medications (n = 1453)	5 (1.9%)[a]	38 (8.2%)[b]	62 (15.4%)[c]	68 (21.0%)[c]
Anticonvulsant medications (n = 1453)	2 (0.8%)[a]	5 (1.1%)[a]	3 (0.7%)[a]	7 (2.2%)[a]
Stimulant medications (n = 1453)	65 (24.6%)[a,b]	136 (29.4%)[b]	81 (20.1%)[a]	25 (7.7%)[c]
Melatonin (n = 1181)	32 (14.2%)[a]	79 (20.0%)[a]	44 (13.5%)[a]	9 (3.8%)[b]
Other medications (omega 3, choline, glutamine, minocycline, buspirone) (n = 1184)	1 (0.4%)[a]	3 (0.8%)[a]	2 (0.6%)[a]	7 (2.9%)[a]

Each superscript letter denotes a subset of diagnostic group whose column proportions do or do not differ significantly from each other at 0.05 level. Same superscript letters across columns indicate no significant difference, while different superscript letters indicate significant differences.
Note: p-values reported in the text are the Bonferroni corrected p-values that have been adjusted for the number of comparisons made.

Pattern of psychotropic medication class prescriptions in individuals with FASD in the presence/absence of another psychiatric disorder

The frequency of use of six categories of medications by individuals with FASD was compared based on the presence/absence of the psychiatric disorders of interest (Supplement, Table S1). Use of antipsychotic medications was higher in individuals with FASD in the presence of comorbid ADHD ($\chi^2(1, n = 1084) = 26.93$, $p < 0.001$), attachment disorder ($\chi^2(1, n = 802) = 27.04$, $p < 0.001$), Autism ($\chi^2(1, n = 395) = 18.84$, $p < 0.001$), conduct disorder ($\chi^2(1, n = 595) = 5.49$, $p = 0.01$), obsessive compulsive disorder (OCD; $\chi^2(1, n = 472) = 6.63$, $p = 0.01$), PTSD ($\chi^2(1, n = 374) = 12.99$, $p < 0.001$), and suicidality ($\chi^2(1, n = 658) = 16.30$, $p < 0.001$). Use of antipsychotics in the presence of comorbid FASD and schizophrenia was marginally significant (Fisher's Exact Test, $p = 0.05$).

Use of antidepressant/anxiolytic medications was higher in individuals with FASD in the presence of comorbid attachment disorder ($\chi^2(1, n = 802) = 16.36$, $p < 0.001$), anxiety disorder ($\chi^2(1, n = 820) = 50.10$, $p < 0.001$), depressive disorders ($\chi^2(1, n = 748) = 37.69$, $p < 0.001$), OCD ($\chi^2(1, n = 471) = 12.71$, $p < 0.001$), personality disorders ($\chi^2(1, n = 349) = 10.22$, $p = 0.001$), PTSD ($\chi^2(1, n = 374) = 14.64$, $p < 0.001$), substance use disorder ($\chi^2(1, n = 660) = 12.08$, $p = 0.001$), and suicidality ($\chi^2(1, n = 658) = 33.01$, $p < 0.001$). Melatonin was more frequently used by individuals with FASD who also had comorbid ADHD ($\chi^2(1, n = 913) = 35.56$, $p < 0.001$), attachment disorders ($\chi^2(1, n = 727) = 20.43$, $p < 0.001$), Tourette syndrome (Fisher's Exact Test, $p < 0.01$), and suicidality ($\chi^2(1, n = 596) = 7.30$, $p < 0.01$).

Use of stimulants was more frequent in the presence of comorbid ADHD ($\chi^2(1, n = 950) = 134.58$, $p < 0.001$), autism ($\chi^2(1, n = 395) = 4.85$, $p = 0.03$), and substance use disorders ($\chi^2(1, n = 660) = 15.24$, $p < 0.001$). Stimulants were less frequently used when a comorbid anxiety disorder was present ($\chi^2(1, n = 820) = 4.60$, $p = 0.03$).

Finally, medications included in the "other" category were more frequently used in the presence of comorbid anxiety disorder (Fisher's Exact Test, $p < 0.01$) and PTSD (Fisher's Exact Test, $p = 0.02$). The frequency of use of these other medications

TABLE 6 Disorders Associated with Psychotropic Medication Class Use

Antipsychotics	Antidepressant/Anxiolytics	Melatonin	Stimulants
ADHD Attachment disorders Autism Conduct disorders OCD PTSD Suicidality	Attachment disorders Anxiety disorders Depressive disorders OCD Personality disorders PTSD Substance use disorders Suicidality	ADHD Attachment disorders Tourette syndrome Suicidality	ADHD Autism Substance use disorders

OCD: Obsessive Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder; ADHD: Attention Deficit Hyperactivity Disorder.

was marginally higher in the presence of comorbid depressive disorders (Fisher's Exact Test, $p = 0.05$) and suicidality (Fisher's Exact Test, $p = 0.05$). Table 6 shows the psychiatric disorders most commonly associated with specific classes of medications in the current sample.

DISCUSSION

The objectives of this study were to describe the types of medications prescribed to individuals with PAE, compare rates of prescriptions between individuals diagnosed with FASD and individuals without FASD as well as how medications are prescribed based on age, sex, and comorbid psychiatric disorders. The results of this study indicate that having a comorbid psychiatric disorder was common and significantly higher in individuals with FASD compared to "at risk" and no FASD participants. In the current study, it was observed that 68.3% of individuals who underwent an FASD assessment had at least one mental health disorder. However, less than 47% were prescribed psychotropic medications. This discrepancy may indicate that individuals who possibly have FASD are undermedicated or that not all individuals require medications. We also observed patterns of a high prevalence of ADHD, anxiety, conduct disorder, depressive disorders, PTSD, schizophrenia, substance use disorder, and suicidality in the FASD + SFF/FASD - SFF groups, which is consistent with the results of recent literature.[10,15,39]

Psychiatric conditions were commonly observed in individuals with FASD.[8,10,39,40] The first research to examine adverse outcomes, including comorbid psychiatric disorders, in individuals with FASD determined that approximately 90% of individuals self-reported having a comorbid mental disorder;[8,40] 65% of individuals with FASD in a correctional setting reported having depression and 43% reported having an anxiety disorder.[41] These previous findings differed with the prevalence of psychiatric disorders in the current sample, where 73.4%–77.6% of individuals with FASD had at least one of the 14 psychiatric disorders. In a study that also used data from the Canadian National FASD Database, which also included participants of all ages, 40.5% of individuals had a diagnosis of a depressive and/or anxiety disorder.[39] One likely explanation for these differences could be the method by which information on psychiatric disorders was collected as well as differing sample sizes between studies. Specifically, Streissguth et al.[8,40] relied exclusively on self-reported presence of psychiatric disorders without confirming the reported diagnoses. This differed with the use of self-reported and/or clinician-diagnosed psychiatric disorders reported in the database for the current study. However, researchers in other studies have found that self-reported mental health is not a substitute for standardized and clinically valid assessment tools.[42,43] While there is preliminary evidence that individuals with FASD could over-report the presence of psychiatric disorders when self-reporting versus clinician-diagnosed disorders, this

has yet to be explored in this population by direct comparison of self-reported and clinician-diagnosed psychiatric disorders. The future research on this topic area should consider, when feasible, the use of clinical assessment tools and interviews when diagnosing and reporting the prevalence of psychiatric disorders to elucidate the true prevalence of psychiatric disorders in this population. Further, the current study considered additional psychiatric disorders than previously published literature,[8,39–41] which could also explain differences in the rates of psychiatric disorders between the current study and past studies.

In the present sample, the FASD + SFF and FASD - SFF groups were more likely to have at least one psychiatric disorder (73.4% and 77.6%, respectively) compared to both "at risk" (52.1%) and no FASD groups (55.3%). Both FASD groups had a significantly higher prevalence of anxiety disorders and depressive disorders compared to the no FASD group. Similarly, the FASD - SFF group had a higher prevalence of schizophrenia compared to the no FASD group. These findings were expected, given the frequency of contributing factors and experience (i.e., childhood adversity and adverse outcomes) associated with the development of these disorders within the FASD population.[10,15,44] Most importantly, results of the present study confirmed that an FASD diagnosis could be associated with a higher prevalence of psychiatric disorders.

It is important to note that despite there being no statistically significant differences between the groups in the prevalence of many of the disorders investigated, there is still clinically meaningful information to glean in these cases. Firstly, the entire sample had confirmed PAE; therefore, an absence of statistically significant differences in prevalence may indicate that PAE is the risk factor for the development of psychiatric disorders while not necessarily meeting the full criteria for an FASD diagnosis. Secondly, it is well known that PAE is often associated with poor social determinants of health and adverse experiences, which, as above, are risk factors for psychiatric disorders.[10,15,44] In addition, adverse childhood experiences, genetic abnormalities, and poor social support occur commonly in FASD and in individuals with mental disorders.[45] Thirdly, the prevalence of psychiatric disorders in our study sample is comparatively higher than general population norms. For example, the high prevalence of bipolar disorders in the two FASD groups and the no FASD group (prevalence ranging from 5.7%-8.8%) in the current study contrasts with the general population prevalence of <1% for Bipolar Type I and <3% for Bipolar Type II.[46] Similarly, rates in the general Canadian population for suicidality (3%-12%),[47] PTSD (9.2%),[48] depressive disorders (5.4%–9.8%),[49] anxiety disorders (4.6%-10.8%),[49] schizophrenia (e.g., psychosis; 1%),[50] and substance use (15.9%)[50] are much lower than in this PAE sample. In addition to indicating higher rates of these psychiatric comorbidities in the FASD population, this data also supports the need for individuals with FASD to be routinely assessed for the presence of psychiatric disorders, and to receive effective treatments, including psychotropic medications, for any diagnosed disorders. It is also noteworthy that the rates of psychiatric disorders in our sample of individuals with FASD were higher compared to individuals with ASD. For example, the rates of depressive disorders (2.0%)[51] and anxiety disorders (7.9%)[51] are lower in individuals with ASD compared to the sample of individuals with FASD in the current study.

Two noteworthy trends concerning medication class prescription rates were observed in our results. First, antipsychotic medication utilization was significantly higher in the FASD group than in the "at risk" group and no FASD group. This finding is insightful, given that previous studies have shown that individuals with FASD are most often prescribed stimulants, followed by antipsychotics.[26,31] We propose that this difference reflects the high prevalence of behavioral disorders in our population sample. The present sample contained more adults than the studies that found more stimulants in their samples.[29] An older sample is likely to have more non-neurodevelopmental disorders, such as schizophrenia.[52]

The use of antipsychotics, such as risperidone, as an adjunctive therapy for pediatric patients and for individuals with FASD with conduct disorder is becoming a well-established practice.[31,53] In a study of paediatric patients with FASD, adding risperidone to their treatment produced a good response to aggression and impulsivity in 80% of cases.[27] Additionally, antipsychotic monotherapy is the most effective approach to manage behavioral disorders in FASD.[27,54] These findings are in line with the current approach to conduct disorder management. In the general population with average or below-average IQ, risperidone is a suitable option for individuals with conduct disorder with severe aggression, or comorbid ADHD with explosive anger.[55] Therefore, in the context of our population, the increased rate of antipsychotic use would be expected. Use of antipsychotics was noticeably higher in the FASD - SFF group than in the FASD + SFF group.

When examining the use of antipsychotics across different disorders in the present sample, the use was higher among individuals with FASD with comorbid attachment disorder, autism, conduct disorder, OCD, PTSD, or suicidality, compared to other disorders. The increased use in OCD and conduct disorder may be related to underlying cognitive inflexibility, which researchers have proposed could be treated with antipsychotics.[26] Similarly, use of antipsychotics could be elevated in autism and conduct disorder to alleviate symptoms of irritability and aggression. Use of antipsychotics could be increased in case of individuals with FASD with comorbid OCD, as the medications could offer benefits to disorganised thoughts and behavior. Moreover, second-generation antipsychotics are used to augment OCD treatment.[56]

The present results also demonstrated a lower level of mood stabilizer use in the FASD group. This decrease could be attributed to the referral process where a comorbid mood disorder could be overlooked in favor of a more overt behavioral or conduct disorder. This may reflect the physician's comfort level in prescribing anticonvulsants as a mood stabilizer, as has been reflected in attitudes and opinions of general practitioners who support individuals with ASD who may require mood stabilizers.[21] Both general practitioners and pediatricians report a low level of comfort when surveyed on this medication class for mood disorders.[57,58] The discomfort could be rooted in inexperience and the need for regular laboratory monitoring, which may limit patient compliance. In turn, it is reasonable that the rate of anticonvulsant use was the lowest in the FASD group.

The present study observed a high prevalence of antidepressants/anxiolytics use, particularly in the two FASD groups, which align with the high prevalence of depressive and anxiety disorders also found in the FASD groups. Importantly, prescription rates of antidepressants and anxiolytics, along with stimulants, follow typical sex differences in the prevalence of depression and ADHD,[34] for which these medications are indicated for use, respectively. Antidepressants and anxiolytics are also commonly prescribed for anxiety disorders, which we also found to be highly prevalent in the current sample. The present sample also reflected a higher use of antidepressants/anxiolytics among individuals with FASD with comorbid attachment disorder, anxiety disorder, OCD, personality disorders, PTSD, substance use disorders, and suicidality. This increased use is in line with the proposed medication algorithm,[26] which recognizes antidepressants/anxiolytics as a treatment for hyperarousal and emotional regulation deficits (attachment disorder, anxiety disorders, PTSD, and personality disorders). Similarly, antidepressants/anxiolytics are a mainstay treatment for OCD.[59] The high use of antidepressants/anxiolytics among individuals with comorbid substance use may be related to underlying comorbid depressive disorder(s).

We also found common use of stimulant medication amongst individuals with FASD. This is to be expected, given that ADHD was prevalent amongst individuals with FASD in the present sample, and has been found to be present in as many as 90% of children with FASD.[12] In their review, Rowles and Findling[60] summarized the results of studies on stimulant interventions for individuals with FASD

which provided evidence of stimulant medication efficacy in reducing ADHD symptoms. However, it is important to note that the efficacy of stimulant medications depends on the stimulant, with dextroamphetamine having a greater effect on inattention compared to methylphenidate.[61,62] Relatedly, stimulants may not be effective in addressing other domains of impairment, such as social skills.[28]

We observed a difference in use of stimulants across the lifespan, with stimulants being more prevalent in transition-aged youth and younger. Children with ADHD tend to have more noticeable symptoms of hyperactivity and impulsivity, waning with age, which may explain the significant difference in prevalence across the lifespan.[63] Clinicians have recognized that providing a stimulant medication is an effective approach to ameliorate the symptoms and dysfunction associated with attention difficulties in younger individuals,[64] which may explain the difference that we observed in the current study. As well, stimulant use was more frequent in the presence of comorbid autism and substance use, and less frequent when a comorbid anxiety disorder was present. The increased incidence of stimulants for autism is likely due to their capacity to reduce symptoms of hyperactivity, inattention, and impulsivity which are known to be prevalent among individuals with autism.[65] The high use of stimulants in cases of substance use disorder may be related to the overrepresentation of substance use disorders in ADHD,[66] for which use of stimulants is the treatment.

We observed a similar difference across the lifespan concerning the use of melatonin. Melatonin is a sleep medication suggested or prescribed to individuals with various sleep issues, such as difficulties in falling asleep and atypical circadian patterns. Within the context of the current sample, it again is not surprising that melatonin was used so frequently, given the common sleep problems found in individuals with FASD.[67] While challenges with sleep at any age can lead to dysfunction,[68] the adverse effects of poor sleep may be particularly noticeable in children and young adults, given that they are often within an educational environment and may have emotion regulation challenges because of still developing self-regulation abilities. These effects can be compounded by the presence of brain domain impairments associated with FASD such as affect regulation, academics, attention, and cognition. Of note, melatonin was more frequently used in individuals with FASD with comorbid ADHD, attachment disorder, Tourette syndrome, and suicidality. ADHD, attachment disorder, and Tourette syndrome are known to be associated with sleep disturbances,[69–71] as is the use of stimulant medications,[71] which may indicate a reason for the common use of melatonin in the current sample. The future medication algorithms should potentially consider how to include sleep in the four clusters of symptoms, or treat it as a separate entity, to optimize how melatonin is used when treating individuals with FASD.

Several limitations to this research must be noted. First, neither effectiveness nor comparability between medications could be commented on, given the data-collection process and the observational nature of this data. A large segment of this population did not have medications recorded. Furthermore, the data did not present reasons for why participants discontinued any previous medication. Purpose, dosages, adverse reactions, and polypharmacy could not be extrapolated. While depression and anxiety are routinely screened for as part of the assessment of the affect regulation brain domain, it is likely that not all mental disorders are queried at the time of assessment. In these cases, there could be an underestimation of prevalence of mental disorder. As some mental disorder diagnoses resulted from prior assessments, we were not certain that previous diagnoses still applied, especially if they were not screened routinely. Under these circumstances, there could be an overestimation of prevalence of mental disorders. Relatedly, if there was no screening of a disorder and no evidence of a prior diagnosis, it was indicated in the database that the disorder was not assessed. While such cases were removed from our data analysis, simply because a disorder was not assessed did not mean that it was not present. Therefore, this created another situation

in which there could be an underestimation of prevalence of mental disorders. Finally, it is possible that the medication data are not truly representative of prescribing habits, as the reported data are based on reports during the FASD assessment process and not after the diagnosis is made when medication adjustments may occur. Future studies should seek to characterize individuals with FASD who receive the various medication classes included in the current study, incorporating analyses that attempt to predict use of medication class based on the brain domains impaired along with adverse outcomes of FASD.

CONCLUSION

Clinically, symptomatic treatment with medications is recognized where formal approval based on sufficient randomized control studies is not available, as is the case in FASD. Individuals with FASD can expect to be treated with antipsychotics, stimulants, antidepressants/anxiolytics, mood stabilizers, and other drugs, as was found in the present study. This is not surprising, given that the manifestation of diverse symptoms in individuals with FASD align with individuals with multiple comorbid conditions, which provide a rationale for pharmacological treatment for individuals with FASD. Melatonin should be considered in both youth and adults with sleep problems and for the algorithmic treatment with psychotropics in FASD. Clinicians should consider prescribing anticonvulsants, given the frequency of mood dysregulation among individuals with FASD. Our findings should give prescribers increased comfort in aligning recognized pharmacological treatment approaches to improve symptoms and functioning for their patients diagnosed with FASD until more high-quality evidence demonstrates otherwise.

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SUPPLEMENT

TABLE S1 Prevalence of Psychotropic Medications According to Psychiatric Disorders in Individuals with FASD.

	Medication Categories and Statistical Significance									
Psychiatric Disorder	**Antipsychotic Medications n (%)**	***p***	**Antidepressant/ Anxiolytic Medications n (%)**	***p***	**Anticonvulsant Medications n (%)**	***p***	**Stimulant Medications n (%)**	***p***	**Melatonin n (%)**	***p***	**Other Medications[¥] n (%)**	***p***
ADHD												
Yes	140 (16.7%)	<0.001	110 (13.1%)	0.74	11 (1.3%)	0.79*	283 (33.7%)	<0.001	134 (19.3%)	<0.001	9 (1.3%)	0.55*
No	25 (6.1%)		51 (12.4%)		4 (1.0%)		16 (3.9%)		22 (5.9%)		3 (0.8%)	
Attachment												
Yes	32 (33.0%)	<0.001	27 (27.8%)	<0.001	2 (2.1%)	0.30*	36 (37.1%)	0.09	25 (32.1%)	<0.001	1 (1.3%)	0.60*
No	90 (12.8%)		88 (12.5%)		7 (1.0%)		202 (28.7%)		83 (12.8%)		7 (1.1%)	
Tourette's												
Yes	0 (0.0%)	0.37*	3 (33.3%)	0.10*	0 (0.0%)	1.00*	3 (33.3%)	1.00*	4 (66.7%)	0.01*	0 (0.0%)	1.00*
No	81 (16.3%)		64 (12.9%)		6 (1.2%)		150 (30.2%)		70 (15.5%)		5 (1.1%)	
Anxiety disorder												
Yes	53 (17.2%)	0.11	90 (29.2%)	<0.001	7 (2.3%)	0.25*	62 (20.1%)	0.03	43 (17.8%)	0.18	7 (2.9%)	**0.01***
No	67 (13.1%)		51 (10.0%)		6 (1.2%)		137 (26.8%)		65 (13.9%)		2 (0.4%)	
Autism												
Yes	14 (50.0%)	<0.001	5 (17.9%)	0.58*	1 (3.6%)	0.36*	14 (50.0%)	0.03	4 (20.0%)	0.54*	0 (0.0%)	1.00*
No	61 (16.6%)		52 (14.2%)		5 (1.4%)		110 (30.0%)		52 (15.8%)		4 (1.2%)	
Bipolar												
Yes	5 (29.4%)	0.21*	6 (35.3%)	0.09*	1 (5.9%)	0.19*	2 (11.8%)	0.17*	1 (8.3%)	1.00*	1 (7.7%)	0.16*
No	5% (17.5%)		53 (16.8%)		3 (1.0%)		88 (27.9%)		38 (13.2%)		3 (1.0%)	
Conduct												
Yes	25 (20.0%)	0.02	24 (19.2%)	0.36	1 (0.8%)	1.00*	37 (29.6%)	0.33	21 (18.9%)	0.31	1 (0.9%)	1.00*
No	56 (11.9%)		74 (15.7%)		3 (0.6%)		119 (25.3%)		65 (15.0%)		4 (0.9%)	
Depressive disorder												
Yes	51 (15.1%)	0.14	86 (25.4%)	<0.001	4 (1.2%)	1.00*	82 (24.3%)	0.51	41 (14.4%)	0.69	6 (2.1%)	0.05*
No	47 (11.5%)		36 (8.8%)		5 (1.2%)		91 (22.2%)		49 (13.4%)		1 (0.3%)	

OCD											
Yes	8 (32.0%)	0.02*	11 (44.0%)	0.001*	1 (4.0%)	0.24*	6 (24.0%)	0.57	5 (31.3%)	0.05*	0 (0.0%)	1.00*
No	60 (13.4%)		72 (16.1%)		4 (0.9%)		131 (29.3%)		54 (13.0%)		5 (1.2%)	
Personality disorder												
Yes	7 (22.6%)	0.30*	12 (38.7%)	0.001	0 (0.0%)	1.00*	7 (22.6%)	0.75	3 (13.0%)	1.00*	1 (4.0%)	0.22*
No	48 (15.1%)		50 (15.7%)		2 (0.6%)		80 (25.2%)		36 (12.6%)		2 (0.7%)	
PTSD												
Yes	26 (28.9%)	<0.001	27 (30.0%)	<0.001	3 (3.3%)	0.09*	20 (22.2%)	0.39	16 (21.9%)	0.06	4 (5.5%)	**0.02***
No	36 (12.7%)		36 (12.7%)		2 (0.7%)		76 (26.8%)		33 (12.9%)		2 (0.8%)	
Schizophrenia												
Yes	6 (33.3%)	0.05*	5 (27.8%)	0.15*	0 (0.0%)	1.00*	1 (5.6%)	0.08*	0 (0.0%)	0.61*	0 (0.0%)	1.00*
No	45 (15.1%)		40 (13.4%)		2 (0.7%)		75 (25.1%)		33 (12.2%)		3 (1.1%)	
Substance use disorder												
Yes	31 (15.3%)	0.33	51 (25.1%)	0.001	5 (2.5%)	0.14*	27 (13.3%)	<0.001	13 (8.1%)	0.08	2 (1.2%)	1.00*
No	57 (12.5%)		64 (14.0%)		4 (0.9%)		124 (27.1%)		57 (13.5%)		7 (1.6%)	
Suicidality												
Yes	41 (25.8%)	<0.001	54 (34.0%)	<0.001	2 (1.3%)	0.64*	36 (22.6%)	0.27	30 (22.2%)	0.01	5 (3.7%)	0.05*
No	62 (12.4%)		68 (13.6%)		4 (0.8%)		135 (27.1%)		59 (12.8%)		5 (1.1%)	

ADHD: Attention Deficit/Hyperactivity Disorder; OCD: Obsessive Compulsive Disorder; PTSD: Post-traumatic Stress Disorder.

**Fisher's Exact test was used instead of Pearson Chi-Square, since at least one cell (25%) has an expected count <5.*

¥*Other medications included omega 3, choline, glutamine, minocycline, and buspirone.*

Sample sizes varied according to psychiatric disorder and medication category within disorders because of missing data. Percentage (%) was calculated based on a valid denominator for each variable in the Table S1. Sample sizes available for medication categories ranged from n = 283–1249.