ORIGINAL RESEARCH

Low hedonic tone and attention-deficit hyperactivity disorder: risk factors for treatment resistance in depressed adults

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Background: The burdens imposed by treatment-resistant depression (TRD) necessitate the identification of predictive factors that may improve patient treatment and outcomes. Because depression and attention-deficit hyperactivity disorder (ADHD) are frequently comorbid and share a complex relationship, we hypothesized that ADHD may be a predictive factor for the diagnosis of TRD. This exploratory study aimed to determine the percentage of undetected ADHD in those with TRD and evaluate factors associated with treatment resistance and undetected ADHD in depressed patients.

Subjects and methods: Adults referred (n=160) for psychiatric consultation completed a structured interview (MINI Plus, Mini International Neuropsychiatric Interview Plus) to assess the presence of psychiatric disorders.

Results: TRD was significantly associated with the number of diagnoses ($P<0.001$), past ($P<0.001$) and present medications ($P<0.001$), chronic anhedonia ($P=0.013$), and suicide ideation ($P=0.008$). Undetected ADHD was present in 34% of TRD patients. The number of referral diagnoses ($P<0.001$), failed medications ($P=0.002$), and past selective serotonin reuptake inhibitor failures ($P=0.035$) were predictive of undetected ADHD in TRD.

Conclusion: Undetected ADHD may be more prevalent among TRD patients than previously thought. In addition, TRD patients are more likely to present with psychiatric comorbidity than non-TRD patients. Screening patients with depression for the presence of ADHD and chronic anhedonia/low hedonic tone may help identify patients with TRD and undetected ADHD and improve treatment outcomes.

Keywords: anhedonia, catecholamine, suicide, dopamine, attention, drug response

Introduction

Major depressive disorder (MDD) affects 10%–15% of the world's population annually and is the leading cause of years of life lived with disability.[1] In the United States alone, MDD affects between 13.1 million and 14.2 million citizens a year.[2] Although considerable progress has been made in the treatment of MDD, research suggests that approximately 30%–40% of patients do not respond to first-line antidepressant therapy, most commonly selective serotonin reuptake inhibitors (SSRIs), and up to 30% of this population does not respond to multiple treatments, and are thereby deemed treatment resistant.[3,4] Moreover, it has been documented that even after treatment, 60%–70% of patients experience residual symptoms commonly associated with depression, and these symptoms are often accompanied by early relapse and increased recurrence rates.[5,6] Thus, given the increasing rates of depression worldwide[7] and the high prevalence of treatment-resistant depression (TRD), identification of clinical features

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that are predictive of TRD is essential to lessen the burden of the disease and develop more effective therapies targeted specifically for patients who do not respond to conventional treatments.

Several studies have demonstrated that rates of comorbidity between attention-deficit hyperactivity disorder (ADHD) and depression range from 22% to as high as 74%.[8–13] In addition, MDD and ADHD share not only common clinical features but also changes in neural pathways that regulate mood.[14–16] ADHD has been suggested as an endophenotype of chronic MDD since both disorders involve dysregulation of dopaminergic and serotonergic function.[10] Collectively, the findings from these studies suggest that MDD comorbid with ADHD may represent a specific neurobiological subtype of depression and lead to the possibility that ADHD may be a predictive factor for the diagnosis of TRD.

Anhedonia, a reduced ability to experience feelings of pleasure, is a key feature of several mood and attention disorders, including MDD and ADHD.[14] The neurobiology of anhedonia is complex and involves a dysfunction in pathways that regulate reward and motivation.[14] Since alterations in these pathways are also observed in several psychopathologies including MDD and ADHD, it has been suggested that the presence of anhedonia may be a predictor of neurobiological subtypes of these disorders and their comorbidities.[14,17] In addition, while *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-V) defines acute anhedonia as a symptom of a major depressive episode;[18] it is plausible that chronic anhedonia, which can be conceptualized as reduced trait hedonic capacity or low hedonic tone (LHT), may be a significant predictor of TRD.[14,19] Furthermore, although research examining the role of anhedonia in ADHD is scant, a recent study conducted on a nonclinical sample of undergraduate students found that LHT partially accounted for the relationship between comorbid MDD and ADHD, highlighting the need to further examine this relationship.[20]

The primary aim of this exploratory study was to determine the proportion of patients with undetected ADHD referred for the treatment of MDD and to identify predictive factors (ie, education, income level, marital status, employment status, perceived social standing, and prior medication use) and clinical features (ie, anhedonia and DSM-IV diagnoses as per the Mini International Neuropsychiatric Interview [MINI] assessment and confirmed by psychiatric consultation) associated with the development of TRD and/or the presence of undetected ADHD. Predictive factors were selected based on prior research suggesting sociodemographic risk factors for the development of ADHD.[21,22] Clinical features were selected to examine the frequency of

comorbidity and potential role of anhedonia on TRD and undetected ADHD. We hypothesized that undetected ADHD is a risk factor for the development of treatment resistance in a subgroup of depressed patients who show residual symptoms when treated with SSRIs. Specifically, this subgroup is hypothesized to have altered neural pathways involved in emotional affect and reward processing.[14,42]

Subjects and methods
Participants and procedure

The sample included 160 participants referred to the START Clinic for Mood and Anxiety Disorders, a tertiary psychiatric center in Toronto, ON, Canada. All new patients referred between July 2011 and 2015 were eligible for participation. As the purpose of the study was to assess predictive factors contributing to the diagnosis of treatment resistance in patients referred for the management of depression, subjects who met the criteria for a major depressive episode in the absence of meeting criteria for bipolar disorder or MDD were excluded from the study. In addition, patients referred for the management of adult ADHD were excluded. Patients were informed that participation in the study was voluntary and that access to treatment was not dependent on enrollment in the study. All participants met the age of consent in Canada (ie, 16 years) and were thus able to provide written informed consent agreeing to have their data used for research purposes. The contents of the self-report package, procedures of data collection, and consent form were all approved by the central institutional review board, Optimum Ethics Review Board.

Information regarding demographic, psychiatric, and medication history was obtained through the START Clinic's standard procedure used to assess new referrals as well as medical notes provided at the time of referral. TRD was defined as a failure to respond to at least two prior adequate trials (dose and duration) of at least two distinctly different classes of antidepressants.[23]

The initial intake assessment involved a multistep process that included the administration of the MINI 6.0.0,[24] the MINI Plus ADHD module 5.0.0,[25,26] a semi-structured clinical psychiatric assessment, and completion of a self-administered questionnaire package including a sociodemographic questionnaire, which asked questions related to gender, age, personal income, ethnicity, marital status, education level, and perceived social standing.

Data gathered during the intake were used by the senior treating psychiatrists (MAK and IE) to establish diagnoses using the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition Text Revision* (DSM-IV-TR) definitions.[27] Patients

referred with the diagnosis of TRD and/or those who met the criteria for major depressive episode (MDE) on the MINI and had not responded adequately to two or more antidepressants during the current episode were identified with TRD.

Assessments and materials

Diagnostic screening and assessment of clinical characteristics

All participants were screened for the presence of psychiatric diagnoses using the MINI[24,26] as well as select MINI Plus modules.[25,26] The MINI is a brief, structured interview designed to assess the presence of DSM-IV and ICD-10 psychiatric illnesses for epidemiology and multicenter studies as well as to track outcomes in non-research clinical settings.[24] The MINI assesses mood, anxiety, somatoform, substance use, psychotic, eating, conduct, and adjustment disorders.[24,26] The MINI has demonstrated good correlation with Structured Clinical Interview for DSM-IV-TR Axis I (κ=0.70 or above) and the Composite International Diagnostic Interview (κ=0.70 or above) for most psychiatric diagnoses.[26,28]

Assessment of the presence of unrecognized ADHD

The DSM-IV-TR defines ADHD as a persistent pattern of inattention and/or hyperactivity–impulsivity, in which six or more symptoms are present for at least 6 months, and several symptoms begin before the age of 12 years.[27] The presence of ADHD was assessed using the ADHD module of the MINI Plus, which assesses lifetime ADHD symptoms as well as symptoms over the past 6 months. Respondents were asked questions pertaining to both child and adult behaviors including symptoms of inattention, hyperactivity, and impulsivity. As there is no "gold standard" ADHD diagnostic tool at present, the MINI Plus has been recommended for the assessment of ADHD during a general assessment of psychiatric disorders in adults. This is designed to ensure ADHD screening commensurate with screening used for other adult psychiatric disorders.[29] All positive scores on the ADHD module were followed up with a clinical interview and review of collateral information.

Assessment of anhedonia

The most common definition of anhedonia is reduced ability to experience pleasure or loss of interest in previously enjoyed activities.[30] Anhedonia was identified using the MINI module A question A2: "were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?" Based on their response, participants were assigned to past, acute (within the past 2 weeks), or chronic (both past and present) categories.

Statistical analyses

Analyses were conducted on the entire sample as well as on a subsample of patients with unipolar TRD and comorbid ADHD. Due to small sample sizes, participants with depression as a secondary diagnosis and bipolar TRD were not analyzed separately. Descriptive statistics were computed, and demographic characteristics and clinical features were compared between TRD and non-TRD cases using Student t-tests for continuous variables and chi-squared tests for all other variables. The association of individual clinical features and comorbid diagnoses with TRD was examined using a chi-squared test for independence. Nominal variables were dichotomized and coded as 0=no and 1=yes based on the absence or presence of symptom or psychiatric diagnosis. To examine the predictive factors of TRD and obtain odds ratio (OR), logistic regression analyses were performed with TRD as the outcome variable and significant clinical features and comorbid diagnoses as independent variables. The presence of anhedonia (past, present, chronic) was compared between those with TRD and comorbid ADHD and TRD alone using chi-squared analyses. All analyses were performed using the Statistical Package for Social Science[31] version 23 (IBM Corporation, Armonk, NY, USA) with statistical significance defined as $P<0.05$.

Results

General characteristics and psychiatric histories

A total of 160 (82 males and 78 females) participants were included in data analysis, of whom, 97 (61%) met the criteria for TRD and 63 (39%) did not. Preliminary data screening indicated that participant age was approximately normally distributed. The assumption of homogeneity of variance was assessed using the Levene's test, which revealed that the assumption of homogeneity was violated, F=4.90, P=0.028. Therefore, results of separate variance t-tests were reported. The mean age differed significantly between the two groups (t[158]=2.12, P=0.036, two-tailed). The mean age of the TRD group (M=39.3, SD=14.3) was about 4.4 years older than the mean age of the non-TRD group (M=34.9, SD=11.7). The effect size as indexed by Cohen's d was 0.34, representing a moderate effect. There were no other significant differences in the characteristics of patients with a diagnosis of TRD and those without (Table 1).

Group comparisons of psychiatric histories between the TRD and non-TRD groups are summarized in Table 2. Statistically significant differences were found in the numbers of psychiatric diagnoses, past medications taken, and psychiatric comorbidities. The mean number of psychiatric

Table I Demographic data of patients with and without TRD

Characteristics	TRD (n=97)	Non-TRD (n=63)	χ^2 or T	P-value[a]
Age at participation, M (SD)	39.3 (14.3)	34.9 (11.7)	2.12	0.036
Range	18–71	17–60		
Gender, n (%)			0.795	0.373
Male	50 (51.5)	37 (58.7)		
Female	47 (48.5)	26 (41.2)		
Marital status, n (%)			5.70	0.337
Single	57 (58.8)	36 (57.2)		
Married	24 (24.7)	12 (19.0)		
Cohabiting	9 (9.3)	4 (6.3)		
Separated/divorced/widowed	3 (3.1)	3 (4.8)		
No response	4 (4.1)	8 (12.7)		
Highest level of education, n (%)	(n=63)	(n=46)	2.97	0.226
High school or less	12 (19.0)	14 (30.4)		
College/university	36 (57.1)	19 (41.3)		
Graduate school	15 (23.8)	13 (28.3)		
Personal income level, n (%)	(n=59)	(n=46)	7.40	0.192
<$25,000	27 (45.8)	14 (30.4)		
$25,000–$49,999	7 (11.9)	8 (17.4)		
$50,000–$74,999	4 (6.8)	7 (15.2)		
$75,000–$99,999	5 (8.5)	3 (6.5)		
≥$100,000	11 (18.6)	5 (10.9)		
Do not know	5 (8.5)	9 (19.6)		

Note: [a]Comparisons evaluated using the two-sample *t*-test for the age of participant and the chi-squared test for all other variables.
Abbreviations: M, mean; TRD, treatment-resistant depression.

diagnoses was higher in the TRD group (M=4.16, SD=1.51) when compared with the non-TRD group (M=2.47, SD=2.02) t[129]=5.54, P<0.001, d=0.95. In addition, the mean number of past medication taken differed significantly with a large effect size observed between the groups (t[158]=3.72, P<0.001, d=0.58). Those in the TRD group (M=2.88, SD=1.56) reported taking more medications than those in the non-TRD group (M=1.76, SD=2.23).

Psychiatric comorbidities are listed in Table 2. The only significant differences between the groups were the presence of bipolar disorder (χ^2 [1]=54.5, P<0.001) and psychotic disorders (χ^2[1]=6.32, P=0.012) in members of the non-TRD group. There was also a significant difference in the proportion of patients diagnosed with ADHD at intake between the groups (χ^2[1]=8.07, P=0.005).

Clinical features of TRD and non-TRD groups

Clinical features of the 97 participants with TRD and the 63 without TRD are summarized in Table 2. Past (91.3%), present (58.7%), and chronic (57.6%) anhedonia, suicide ideation (65.2%), SSRI failure (48.5%), and suicide attempt (17.4%) were among the common features observed in patients with TRD. Further analyses revealed a significant association between past SSRI response and the presence or absence of current anhedonia (χ^2 [1]=9.76, P=0.002, Φ=0.326) and chronic anhedonia (χ^2 [1]=10.9, P=0.001, Φ=0.345). The odds of failing to respond adequately to previous SSRI treatment were approximately 4.07-fold higher among individuals who reported a current episode of anhedonia at the time of intake and 4.42-fold higher in those with chronic anhedonia. Undetected ADHD (χ^2 [1]=5.37, P=0.020, Φ=0.235) and social phobia (χ^2 [1]=8.11, P=0.004, Φ=0.289) were also significantly associated with SSRI failure. The odds of failing SSRI treatment were 4.07-fold higher among those with undetected ADHD and 4.81-fold higher among those who met the criteria for social phobia. There was no significant association with past anhedonia, nor other comorbid diagnoses reported at intake.

Compared with those diagnosed with TRD, a significantly smaller proportion of patients without a diagnosis of TRD reported anhedonic features: past anhedonia (χ^2 [1]=13.8, P<0.001, OR=5.25), present (χ^2 [1]=6.91, P=0.009, OR=2.41), chronic (χ^2 [1]=6.24, P=0.013, OR=2.30), and suicide ideation (χ^2 [1]=7.01, P=0.008, OR=1.76). As summarized in Table 2, the frequency of other clinical features did not differ significantly between patients with and without TRD (all P>0.05).

Table 2 Psychiatric history of patients with and without TRD

	TRD (n=97)	Non-TRD (n=63)	χ^2 or T	P-value[a]
Number of psychiatric diagnosis, M (SD)	4.16 (1.51)	2.47 (2.02)	5.54	<0.001
Number of past medications, M (SD)	2.88 (1.56)	1.76 (2.23)	3.72	<0.001
Past SSRI failure, n (%)			1.26	0.262
Yes	42 (43.3)	21 (33.3)		
No	55 (56.7)	39 (61.9)		
Number of past SSRIs, M (SD)	0.85 (1.13)	0.82 (1.42)	0.155	0.877
Suicide score assessment based on the MINI, M (SD)	4.32 (7.67)	4.08 (6.20)	0.201	0.491
Suicide ideation assessment based on the MINI, n (%)	60 (65.2)	32 (51.6)	7.01	0.008
Suicide attempt assessment based on the MINI, n (%)	16 (17.4)	15 (24.2)	1.07	0.302
Anhedonia assessment based on the MINI, n (%)				
Past episode	84 (91.3)	42 (67.7)	13.8	<0.001
Present episode	54 (58.7)	23 (37.1)	6.91	0.009
Chronic (LHT)	53 (57.6)	23 (37.1)	6.24	0.013
Psychiatric comorbidities,[b] n (%)				
Generalized anxiety disorder	79 (81.4)	44 (69.8)	2.89	0.089
Social phobia	52 (53.6)	36 (57.1)	0.193	0.661
Agoraphobia	31 (32.0)	26 (41.3)	1.44	0.230
Panic disorder	31 (32.0)	25 (39.7)	1.00	0.317
Bipolar	0 (0)	29 (46.0)	54.5	<0.001
OCD	21 (21.6)	22 (34.9)	3.42	0.064
PTSD	15 (15.5)	3 (4.8)	1.75	0.186
Alcohol dependence and abuse	8 (11.3)	10 (15.9)	2.22	0.136
Substance dependence and abuse	11 (8.2)	7 (11.1)	0.067	0.795
Bulimia nervosa	2 (2.1)	5 (7.9)	3.15	0.076
Anorexia nervosa	1 (1)	1 (1.6)	0.096	0.757
Psychotic disorders	0	4 (6.3)	6.32	0.012
Specific phobia	10 (10.3)	6 (9.5)	0.026	0.871
ADHD	33 (34)	26 (41.2)	8.07	0.005

Notes: [a]Comparisons were evaluated using the two-sample t-test for the number of diagnoses, past medications, past SSRI failures, and the Chi-squared test for all other variables. [b]Psychiatric diagnoses were assessed using the MINI at the time of intake interview and confirmed by treating psychiatrist. The number of past medications, past SSRIs, and number of past SSRIs were assessed during the intake interview in combination with referral documentation.
Abbreviations: ADHD, attention-deficit hyperactivity disorder; LHT, low hedonic tone; M, mean; MINI Plus, Mini International Neuropsychiatric Interview Plus; OCD, obsessive and compulsive disorder; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression.

Of the 97 patients with TRD, 33 (34%) met the criteria for undetected ADHD when compared with eight (12.7%) non-TRD cases. The Chi-squared analyses demonstrated that there were significant associations between unrecognized ADHD and number of disorders (χ^2 [5]=37.1, P<0.001, V=0.619, OR=4.15), number of failed medications (χ^2 [7]=22.7, P=0.002, V=0.486, OR=1.65), past SSRI failure (χ^2 [1]=5.37, P=0.020, Φ=0.235, OR=2.74), and number of failed SSRIs (χ^2 [5]=12.0, P=0.035, V=0.035, OR=1.59). Furthermore, social phobia (χ^2 [1]=19.6, P<001, Φ=0.450, OR=9.33), obsessive–compulsive disorder (χ^2 [1]=4.03, P=0.045, Φ=0.204, OR=2.70), and generalized anxiety disorder (χ^2 [1]=5.17, P=0.023, Φ=0.231, OR=5.17) were significantly associated with undetected ADHD in the TRD population. In addition, 67% of patients with both TRD and ADHD also had chronic anhedonia.

The presence of past, present, and chronic anhedonia in participants with TRD and patients with TRD and ADHD are shown in Figure 1. The percentage of anhedonic classification across all the three groups was higher among the TRD with comorbid ADHD group when compared with TRD-alone cases. However, these differences were not significant (P>0.05).

Discussion
Main findings

This study has demonstrated that approximately one-third of patients with TRD had previously undetected ADHD and two-thirds of patients with both TRD and ADHD also had chronic anhedonia or LHT. Factors associated with undetected ADHD in TRD patients were the number of failed medications at intake, past SSRI failure, and the number of failed SSRIs. Furthermore, features associated with the presence of ADHD in the TRD population included common comorbidities often seen in the ADHD population alone. These include social phobia, obsessive–compulsive
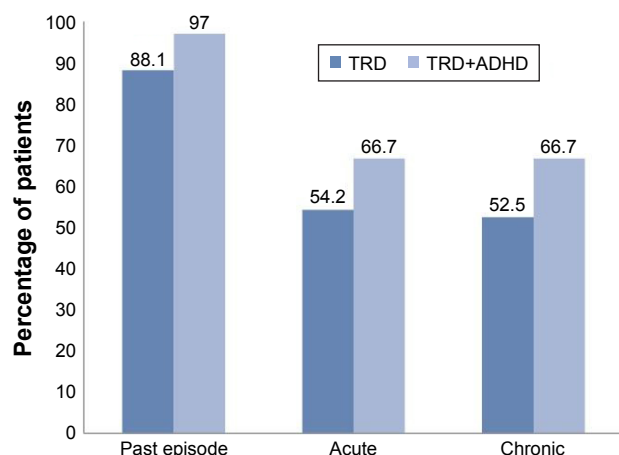
Figure 1 Comparison of anhedonic features between the TRD-alone and TRD/ADHD groups.
Note: A comparison of anhedonic features between the TRD-alone (n=59) and TRD with comorbid ADHD (n=33) groups.
Abbreviations: ADHD, attention-deficit hyperactivity disorder; TRD, treatment-resistant depression.

disorder, and generalized anxiety disorder,[32–37] suggesting that ADHD has a potentially important role in TRD patient populations.

Despite advances in the treatment of depression, the incidence of TRD remains high. Therefore, the identification of clinical features that might predict TRD is an important step toward lessening the burden of depression and improving patient outcomes. Previous studies have shown that ADHD is often comorbid with depression[8–12] and that the prevalence of ADHD symptoms is positively correlated with clinical stages of depression.[10] In the current study, previously undetected ADHD was detected in 34% of patients with TRD. The number of failed medications at intake, past SSRI failure, and the number of failed SSRIs were significantly associated with undetected ADHD in TRD patients, suggesting that the presence of ADHD may be indicative of resistance to antidepressants, specifically SSRIs. This concept is supported by the results of a study conducted by Chen et al,[38] who demonstrated that patients with MDD and comorbid ADHD had an increased risk of treatment resistance to antidepressants compared with patients with MDD only. Furthermore, patients with MDD and ADHD who had a standard ADHD treatment exhibited a similar risk of resistance to antidepressants compared with those with MDD only. Collectively, the findings of the current study and data from the aforementioned studies suggest that undetected ADHD may be a predictor of TRD and that treatment of the underlying ADHD may improve outcomes for patients with TRD. This may be attributable to the inhibitory effects of the serotonin system, specifically via the activation of

serotonin$_{2A}$ and serotonin$_{2C}$ receptors, on the dopaminergic and noradrenergic systems, respectively.[39–41]

Although this study did not investigate neural correlates that link ADHD and TRD, it has been demonstrated that the two disorders share chronic anhedonia as a manifestation of LHT and changes in neural pathways that regulate reward processing as an underlying feature.[13] Both TRD and ADHD are characterized by altered sensitivity to reinforcement, which is accompanied by changes in neural pathways that regulate feelings of reward and pleasure. These same pathways have also been implicated in the regulation of hedonic tone.[14] Dysfunction in the primary neural pathway that modulates emotional affect, comprising the limbic–cortical–striatal–pallidal–thalamic circuits,[37] has been implicated as playing a role in both MDD and ADHD. For example, depression is associated with frontal hypometabolic activity, accompanied by hypermetabolic activity in the ventromedial prefrontal cortex and subgenual anterior cingulate cortex.[43–46] In patients with ADHD, significant hypoactivity has been demonstrated in several frontal regions including orbitofrontal, inferior prefrontal, dorsolateral prefrontal, and anterior cingulate cortices.[47] Activation of these pathways is also altered in patients with LHT, suggesting that these circuits may represent the neural correlate linking anhedonia, TRD, and ADHD.[14] The finding of our study that 67% of patients with both TRD and ADHD had chronic anhedonia supports the suggestion that trait LHT may be the underlying feature linking TRD and ADHD.

Current neurobiological research supports similar morphological and functional abnormalities in brain volume, deactivation of the frontal regions of the brain,[48,49] and deficits in reward processing. To further elucidate the neurobiological overlap, functional imaging studies, psychopharmacological interventions, tasks assessing default-mode network dysfunction (eg, the two-back test),[50] and neurotransmitter studies should be conducted in psychiatric populations with comorbid ADHD and MDD.

Limitations and future directions

There are some limitations of this study that should be considered. First, the study design was cross-sectional and used self-report lifetime histories of symptoms and suicidal behavior; therefore, causal or directional relationships cannot be inferred from these findings.[51] There is limited research that has evaluated the prevalence and associations of undetected adult ADHD and treatment resistance in the clinical population, and to our knowledge, no studies have evaluated the role of chronic anhedonia or LHT as a transdiagnostic link

between ADHD and treatment resistance in this population. Thus, a cross-sectional approach provided an opportunity to examine potentially important explanations for TRD and its association with ADHD. Given the exploratory and cross-sectional nature of this study, this study should be replicated using a prospective longitudinal approach to elucidate the implied causal associations.

Second, the study relied on self-reported data, and given the stigma associated with suicide, it is possible that suicidal behavior was underreported. However, previous studies suggest that self-reported depressive and suicidal symptom scales are valid and reliable within the ADHD population.[52] Moreover, since this sample was referred and largely Caucasian, our findings may not be generalizable to community samples or other ethnic groups. Future research should continue to investigate the role of LHT in etiology and treatment implications across a scope of psychological disorders including posttraumatic stress, substance abuse, and anxiety disorders.

Conclusion

This study demonstrated that individuals with TRD are significantly more likely to have a higher number of comorbid psychiatric disorders, including ADHD, compared with non-TRD individuals. In addition, despite limitations with the self-report measure of past anhedonia used in the current study, results suggest that trait anhedonia or LHT may represent a link between TRD and ADHD, which could be predictive of poorer treatment outcomes in a subset of patients treated with SSRIs. These findings emphasize the importance of screening depressed patients who fail SSRI treatment for ADHD and LHT to help identify patients with TRD and provide improved clinical outcomes.

Disclosure

Irvin Epstein has been a consultant or speaker's bureau member of Janssen-Ortho Inc. and has participated in clinical trials for Bristol-Myers Squibb, Takeda, Shire, Pfizer, Roche, Purdue, Janssen Inc., and Forest. Martin A Katzman has been a consultant or advisory board member of GlaxoSmithKline, Lundbeck, Eli Lilly, Boehringer Ingelheim, Organon, Astra Zeneca, Jannsen-Ortho, Solvay, Bristol-Myers Squibb, Shire, Sunovion, Pfizer, Purdue, Merck, Astellas, and Bedrocan. He has undertaken research for GlaxoSmithKline, Lundbeck, Eli Lilly, Organon, AstraZeneca, Jannsen-Ortho, Solvay, Genuine Health, Shire, Bristol-Myers Squibb, Takeda, Pfizer, Hoffman La Roche, Biotics, Purdue, Astellas, Jannsen-Ortho, and Forest. He has received honoraria from GlaxoSmithKline, Lundbeck, Eli Lilly, Boehringer Ingelheim, Organon, Astra Zeneca, Janssen-Ortho, Solvay, Bristol-Myers Squibb, Shire, Sunovion, Pfizer, Purdue, Merck, Astellas, and Bedrocan. He has received research grants from CIHR, Sick Kids Foundation, Center for Addiction and Mental Health Foundation, Canadian Psychiatric Research Foundation, Canadian Foundation for Innovation, and the Lotte & John Hecht Memorial Foundation. Tia Sternat, Kathryn Fotinos, and Alexa Fine report no conflicts of interest in this work.

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