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Total and differential white blood cell counts, inflammatory markers, adipokines, and incident metabolic syndrome in phase 1 of the clinical antipsychotic trials of intervention effectiveness study

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ABSTRACT

Objective: The metabolic syndrome is highly prevalent in patients with schizophrenia. We previously found that blood C-reactive protein (CRP), interleukin-6 (IL-6), and leptin levels were predictors of current metabolic syndrome in schizophrenia. In the present study, we investigated whether baseline levels of total and differential white blood cell (WBC) counts, inflammatory markers, and adipokines predicted incident metabolic syndrome in schizophrenia.

Method: For subjects from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial who did not have metabolic syndrome at baseline (n = 726), WBC counts, inflammatory markers, and adipokines were investigated as predictors of incident metabolic syndrome over 12 months of antipsychotic treatment. Cox proportional hazards regression models, controlling for multiple potential confounding factors, were used to investigate these associations.

Results: 39% of subjects (n = 280) had incident metabolic syndrome over 12 months. After controlling for potential confounders, baseline blood IL-6 (HR = 1.12, 95% CI 1.01–1.24, p = 0.031) and leptin (HR = 1.12, 95% CI 1.01–1.24, p = 0.038) were significant predictors of incident metabolic syndrome, and there was a trend-level association with CRP (HR = 1.09, 95% CI 1.00–1.19, p = 0.059).

Conclusions: Our findings provide additional evidence that measurement of inflammatory markers and adipokines are germane to the clinical care of patients with schizophrenia. Specifically, these markers may identify—prior to treatment—patients with schizophrenia at heightened risk for incident adverse cardiometabolic effects of antipsychotics. Given the tremendous burden of cardiovascular disease morbidity and mortality in schizophrenia, vigilant screening for and treatment of metabolic risk factors in this patient population are warranted.

1. Introduction

A significant gap exists between the mortality rates of patients with schizophrenia and the general population, and it has worsened in recent decades (Saha et al., 2007). Some of this mortality gap may be attributable to side effects of treatment (McEvoy et al., 2005). The metabolic syndrome is comprised of a group of risk factors for the development of atherosclerotic cardiovascular disease, type 2 diabetes (Grundy et al., 2005), and cardiovascular disease mortality (Galassi et al., 2006). Based on American Heart Association criteria (Grundy et al., 2005), the metabolic syndrome is common in patients with schizophrenia, with a prevalence of 43% in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (McEvoy et al., 2005). Thus, a high proportion of patients with schizophrenia are at increased risk for mortality associated with the metabolic syndrome.

A growing body of evidence suggests an association between inflammation and the metabolic syndrome in schizophrenia. Both the metabolic syndrome and schizophrenia are associated with states of chronic inflammation (Beumer et al., 2012; Devaraj et al., 2010; Mori et al., 2015). The acute phase reactant C-reactive protein (CRP) has been demonstrated as an independent predictor of cardiovascular disease in a meta-analysis (Devaraj et al., 2010), and as a predictor of current metabolic syndrome (Mori et al., 2015) in patients with schizophrenia. Elevated CRP levels have also been associated with treatment-resistant symptoms in patients with schizophrenia (Fond et al., 2018a, 2018b). Increased waist circumference and hypertriglyceridemia in patients with schizophrenia is also associated with increased risk for hyperuricemia, and subsequent inflammation (Godin

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et al., 2015). Furthermore, there is evidence for alterations in inflammatory markers in patients with schizophrenia compared to controls, including cytokines (Miller et al., 2011), lymphocytes (Miller et al., 2013a), and CRP (Miller et al., 2014). Other studies have found an association between white blood cell counts and metabolic syndrome criteria in both the general population (Kim et al., 2008; Lao et al., 2008) and in patients with schizophrenia (Fan et al., 2010; Miller et al., 2013b, 2015). Notably, one study found that total WBC counts were positively correlated with both increased risk of metabolic syndrome and more severe psychopathology in schizophrenia (Fan et al., 2010).

Although personalized medicine approaches that utilize biomarkers to guide treatment for patients has seen success in other fields of medicine, much progress still needs to be made for those with schizophrenia (Buckley and Miller, 2017). Recent studies have provided evidence for an association between inflammation in the peripheral blood and metabolic disturbance in patients with schizophrenia, suggesting a potential role for these markers in guiding the selection of treatment in patients with schizophrenia (Mori et al., 2015; Beumer et al., 2012). We previously found that blood inflammatory marker levels were associated with prevalent (i.e., current) metabolic syndrome at the baseline visit in the CATIE schizophrenia trial (Mori et al., 2015). However, whether baseline blood inflammatory markers predict incident (i.e., new-onset) metabolic syndrome following antipsychotic treatment has not been investigated. Positive findings in this area may identify—prior to treatment—patients with schizophrenia at heightened risk for incident adverse cardiometabolic effects of antipsychotics.

2. Methods

Data used in this study were obtained from the publicly available limited access CATIE schizophrenia trial dataset. The study was deemed exempt by the Augusta University IRB. A full description of the CATIE schizophrenia trial has been previously described (Lieberman et al., 2005). Baseline total and differential WBC, inflammatory markers (CRP, IL-6, E-Selectin, ICAM-1, and VCAM-1), and adipokines (adiponectin and leptin) were derived from blood samples collected at baseline/screening. Details on assay methodology have been described elsewhere (Meyer et al., 2009). Briefly, plasma levels of markers were measured using a multiplex immunosorbent assay (ELISA). Plasma CRP levels were measured using a separate ELISA. CBC with differential, and fasting blood glucose and lipid panels were analyzed at baseline and at 3, 6, and 12 months by standard clinical laboratory assays. Waist circumference and blood pressure were also measured at baseline and again at 3, 6, and 12 months. We excluded subjects taking scheduled oral antibiotics, non-steroidal anti-inflammatory drugs, corticosteroids, and/or other immunomodulatory agents within two weeks of the baseline study visit. We also excluded subjects taking scheduled anti-diabetic, anti-hypertensive, and/or anti-hyperlipidemic drugs at study baseline. Data on the following baseline covariates were also available: age, sex, race, smoking (number of cigarettes/day in the past week), fasting status, alcohol (based on the Clinician Alcohol Use Scale), and illicit drug use (based on the Clinician Drug Use Scale), antipsychotic medication (intent-to-treat), antidepressant treatment, mood stabilizer treatment, and number of metabolic syndrome criteria met at study baseline.

Metabolic syndrome status was determined based on the criteria outlined by the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (Grundy et al., 2005). The presence of the metabolic syndrome was defined as the subject meeting three or more of the following five criteria at a given time point: 1) waist circumference ≥ 102 cm in males or ≥88 cm in females, 2) fasting triglycerides ≥ 150 mg/dL, 3) fasting HDL < 40 mg/dL in males or <50 mg/dL in females, 4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg (or antihypertensive treatment), 5) fasting glucose ≥ 100 mg/dL.

The data were analyzed using SPSS version 24 (SPSS, Inc.; Chicago, Illinois). We included all subjects from the CATIE study with baseline blood inflammatory markers who did not have the metabolic syndrome (i.e., meeting ≤2 criteria) at baseline. Metabolic syndrome status (yes/no) was assessed at 3, 6, and 12 months. All blood markers were found to be non-normally distributed (using a one-sample Kolmogorov-Smirnov test), and were log transformed prior to the analyses. Cox proportional hazards regression models were used to assess baseline values of blood markers as predictors of incident metabolic syndrome over 12 months of treatment for all subjects, controlling for potential confounding effects of age, sex, race, smoking, fasting status, alcohol, illicit drug use, antipsychotic, antidepressant, and mood stabilizer treatment, and number of metabolic syndrome criteria met at baseline. Several post-hoc analyses were performed. For blood markers associated with metabolic syndrome risk with $p < 0.10$, we investigated these markers as predictors of individual metabolic syndrome criteria. We also performed Cox proportional hazards regression analyses for each medication (intent-to-treat) in the CATIE study (perphenazine, ziprasidone, quetiapine, risperidone, and olanzapine), separately, to examine antipsychotic-specific effects. For all analyses, results were considered statistically significant at the $\alpha = 0.05$ level (two-sided). Given the preliminary nature of this study, we did not correct *p*-values for multiple comparisons.

3. Results

The demographic and clinical characteristics of the study sample are presented in Table 1. A total of 726 subjects who did not meet the criteria for metabolic syndrome (≤2 of 5 criteria) at study baseline were included. The number of subjects with available data on blood markers ranged from 560 (for adiponectin) to 705 (for ICAM) with a mean of 678 subjects per marker (93%). Data on smoking were available for 708 subjects, and alcohol and drug use information for 722 subjects. At 3 months, n = 155 (21.3%) of subjects met criteria for the metabolic syndrome. The cumulative prevalence of the metabolic syndrome at 6 and 12 months was 32.1% and 38.9%, respectively. Subjects with incident metabolic syndrome (n = 280) had significantly lower baseline CRP, and higher baseline IL-6 and leptin levels at baseline compared to subjects who did not develop metabolic syndrome (n = 446; $p < 0.01$ for each). Otherwise, there were no differences in age, sex, race, smoking, substance use, antidepressant treatment, or mood stabilizer treatment based on metabolic syndrome status at study endpoint ($p > 0.05$ for each).

In unadjusted Cox proportional hazards regression models, baseline CRP (HR = 1.11, 95% CI 1.03–1.20, p = 0.007), IL-6 (HR = 1.16, 95% CI 1.06–1.28, p = 0.002), and leptin (HR = 1.14, 95% CI 1.05–1.25, p = 0.002) levels were significant, positive predictors of incident metabolic syndrome (see Table 2). After controlling for potential confounders, baseline blood IL-6 (HR = 1.12, 95% CI 1.01–1.24, p = 0.031) and leptin (HR = 1.12, 95% CI 1.01–1.24, p = 0.038) remained significant predictors of incident metabolic syndrome, and there was a trend-level association with CRP (HR = 1.09, 95% CI 1.00–1.19, p = 0.059). Neither total nor differential WBC counts, E-Selectin, VCAM, nor adiponectin predicted incident metabolic syndrome.

In post-hoc analyses, we investigated CRP, IL-6, and leptin as predictors of individual components of the metabolic syndrome. Baseline blood CRP was a significant predictor of high triglycerides (HR = 1.12, 95% CI 1.02–1.22, p = 0.020) and low HDL (HR = 1.14, 95% CI 1.03–1.27, p = 0.010). IL-6 was a significant predictor of increased waist circumference (HR = 1.41, 95% CI 1.16–1.72, p = 0.001) and low HDL (HR = 1.13, 95% CI 1.00–1.27, p = 0.044). Leptin was also a significant predictor of increased waist circumference (HR = 1.60, 95% CI 1.28–2.00, $p < 0.001$) and low HDL (HR = 1.15, 95% CI 1.01–1.31, p = 0.030). None of these parameters was a predictor of the blood pressure or glucose criteria.

Table 1
Demographic and laboratory characteristics of the study sample.

Variable	Total	Metabolic syndrome		p-value[a]
	(N = 726)	Yes (n = 280)	No (n = 446)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	38.1 (11.3)	39.0 (10.7)	37.6 (11.6)	0.09
Smoking (cigarettes/day)	12.2 (13.7)	12.0 (14.1)	12.3 (13.4)	0.77
WBC ($\times 10^3/\mu L$)	6.9 (2.3)	6.9 (2.1)	7.0 (2.5)	0.69
Neutrophils ($\times 10^3/\mu L$)	4.3 (1.9)	4.2 (1.6)	4.3 (2.1)	0.75
Lymphocytes ($\times 10^3/\mu L$)	2.0 (0.7)	2.0 (0.7)	2.0 (0.7)	0.40
Monocytes ($\times 10^3/\mu L$)	0.44 (0.19)	0.45 (0.19)	0.44 (0.18)	0.27
Eosinophils ($\times 10^3/\mu L$)	0.19 (0.19)	0.19 (0.17)	0.19 (0.21)	0.77
E-Selectin (pg/mL)	26,729 (27739)	27,229 (23829)	26,414 (29960)	0.19
VCAM (pg/mL)	1,057,672 (503758)	1,037,609 (475352)	1,070,532 (521292)	0.53
ICAM-1 (pg/mL)	334,081 (303096)	315,805 (222774)	345,769 (344540)	0.60
Adiponectin (pg/mL)	14,027,276 (9330773)	13,112,846 (9330773)	14,618,967 (10368603)	0.08
CRP (pg/mL)	982,079 (4855400)	926,092(1427073)	1,017,779 (6110868)	<0.01
IL-6 (pg/mL)	85.7 (143.9)	93.7 (123.7)	80.6 (155.4)	<0.01
Leptin (pg/mL)	1249 (1452)	1500 (1712)	1081 (1222)	<0.01
Variable	Total	Metabolic syndrome		p-value[b]
	(N = 726)	Yes (n = 280)	No (n = 446)	
	n (%)	n (%)	n (%)	
Sex				
Male	563 (77.5)	208 (74.3)	355 (79.6)	0.10
Female	163 (22.5)	72 (25.7)	91 (20.4)	
Race				0.27
White	405 (55.8)	161 (57.5)	244 (54.7)	
Black	297 (40.9)	104 (37.1)	193 (43.3)	
Native American	13 (1.8)	7 (2.5)	6 (1.3)	
Asian	19 (2.6)	7 (2.5)	12 (2.7)	
Pacific Islander	4 (0.6)	3 (1.1)	1 (0.2)	
Antidepressant	194 (26.7)	79 (28.2)	115 (25.8)	0.49
Mood stabilizer	91 (11.4)	36 (11.7)	55 (11.2)	0.91
Alcohol use				
Abstinent	441 (61.1)	164 (58.6)	277 (62.7)	0.86
Use without impairment	219 (30.3)	88 (31.4)	131 (29.6)	
Abuse or dependence	62 (8.6)	28 (10.0)	34 (7.6)	
Drug use				
Abstinent	514 (71.2)	202 (72.1)	312 (70.6)	0.42
Use without impairment	125 (17.3)	48 (17.1)	77 (17.4)	
Abuse or dependence	83 (11.5)	30 (10.7)	53 (12.0)	
Metabolic syndrome				
Criteria met at baseline				
0	186 (25.6)	47 (16.8)	139 (31.2)	<0.01
1	284 (39.1)	108 (38.6)	176 (39.5)	
2	256 (35.3)	125 (44.6)	131 (29.4)	
Metabolic syndrome at 3 months	155 (21.3)			
Metabolic syndrome at 6 months	233 (32.1)			
Metabolic syndrome at 12 months	280 (38.9)			

Student's *t*-test, 2-sided.
[a] Mann-Whitney *U* test was used for all comparisons, except age, which was analyzed using.
[b] Fisher's Exact Test, 2-sided was used for all comparisons.

In additional post-hoc analyses, we investigated blood markers as predictors of incident metabolic syndrome for each antipsychotic medication (intent-to-treat) in the CATIE study, considered separately (see Table 2). Baseline CRP predicted incident metabolic syndrome in patients treated with risperidone (HR = 1.26, 95% CI 1.05–1.50, p = 0.012). Baseline leptin levels predicted incident metabolic syndrome for patients treated with ziprasidone (OR = 2.11, 95% CI 1.20–3.71, p = 0.009).

4. Discussion

We found that after controlling for potential confounders, baseline blood IL-6 and leptin levels predicted new-onset incident metabolic syndrome over 12 months in patients with chronic schizophrenia in the CATIE trial, and baseline blood CRP levels were associated with metabolic syndrome risk at the trend level. When considering individual metabolic syndrome criteria, these association were stronger for increased waist circumference and dyslipidemia than for changes in blood pressure or glucose. Incident metabolic syndrome over the first year of the CATIE trial was also a common phenomenon, affecting 39% of at-risk subjects. The present findings complement and extend our previous work, which found that blood CRP, interleukin-6, and leptin levels were significant predictors of current metabolic syndrome at the baseline visit of the CATIE trial (Mori et al., 2015), suggesting a broader clinical utility of these markers.

In post-hoc analyses, we found some evidence for differential effects of specific antipsychotics on the association between inflammatory markers and incident metabolic syndrome. Baseline CRP predicted incident metabolic syndrome patients treated with risperidone and olanzapine. Baseline leptin levels also predicted incident metabolic syndrome for patients treated with ziprasidone. These findings are consistent with previous findings in the CATIE trial that blood inflammatory markers were differentially affected by antipsychotic regimens (Meyer et al., 2009). However, they are in contrast with a cross-sectional

Table 2
Cox regression analyses of blood markers as predictors of incident metabolic syndrome.

a All subjects (n=726)

	Metabolic Syndrome	
Parameter	HR (95% CI)	p-value
WBC	0.82 (0.55-1.24)	0.350
Neutrophils	0.89 (0.66-1.20)	0.439
Monocytes	1.03 (0.78-1.36)	0.843
Lymphocytes	0.80 (0.53-1.21)	0.300
Eosinophils	1.03 (0.89-1.20)	0.689
E-Selectin	1.04 (0.90-1.21)	0.611
VCAM	0.96 (0.77-1.19)	0.681
ICAM	0.91 (0.77-1.09)	0.315
Adiponectin	0.89 (0.71-1.10)	0.263
CRP	1.09 (0.97-1.82)	0.059
IL-6	1.12 (1.01-1.24)	***0.031***
Leptin	1.12 (1.01-1.24)	***0.038***

b Individual antipsychotics

	Perphenazine (n=135)		Ziprasidone (n=93)		Quetiapine (n=160)		Risperidone (n=173)		Olanzapine (n=165)	
Parameter	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
WBC	1.06 (0.28-3.99)	0.933	0.48 (0.11-2.08)	0.329	0.57 (0.22-1.53)	0.267	1.19 (0.54-2.61)	0.669	0.86 (0.39-1.89)	0.712
Neutrophils	1.23 (0.43-3.55)	0.702	0.37 (0.10-1.34)	0.131	0.68 (0.34-1.35)	0.270	1.01 (0.59-1.74)	0.965	0.97 (0.54-1.71)	0.903
Monocytes	1.51 (0.52-4.45)	0.451	1.39 (0.49-3.94)	0.534	1.01 (0.53-1.95)	0.972	1.29 (0.80-2.08)	0.301	0.80 (0.44-1.44)	0.449
Lymphocytes	0.87 (0.28-2.74)	0.815	0.75 (0.19-2.96)	0.680	0.68 (0.24-1.88)	0.452	1.48 (0.62-3.50)	0.375	0.64 (0.29-1.40)	0.260
Eosinophils	0.71 (0.46-1.10)	0.126	1.31 (0.77-2.20)	0.317	0.92 (0.63-1.33)	0.641	1.16 (0.86-1.56)	0.342	1.30 (0.95-1.78)	0.100
E-Selectin	0.91 (0.56-1.46)	0.683	1.13 (0.66-1.94)	0.665	0.97 (0.71-1.33)	0.840	1.03 (0.76-1.39)	0.842	1.29 (0.74-1.76)	0.110
VCAM	0.59 (0.27-1.31)	0.196	0.51 (0.17-1.47)	0.211	1.11 (0.70-1.75)	0.667	0.97 (0.63-1.52)	0.906	1.14 (0.67-1.93)	0.629
ICAM	0.53 (0.27-1.05)	*0.067*	0.58 (0.27-1.24)	0.156	1.01 (0.73-1.38)	0.973	0.94 (0.62-1.41)	0.762	1.13 (0.74-1.72)	0.570
Adiponectin	0.81 (0.31-2.09)	0.657	0.32 (0.08-1.24)	0.100	0.98 (0.66-1.46)	0.924	0.82 (0.52-1.29)	0.383	0.94 (0.60-1.49)	0.800
CRP	0.97 (0.71-1.32)	0.834	0.97 (0.71-1.32)	0.830	1.01 (0.85-1.20)	0.926	1.26 (1.05-1.50)	***0.012***	1.12 (0.93-1.35)	0.249
IL-6	1.28 (0.89-1.83)	0.187	1.17 (0.76-1.81)	0.479	1.15 (0.93-1.41)	0.193	1.10 (0.90-1.34)	0.357	1.11 (0.88-1.39)	0.369
Leptin	1.09 (0.83-1.43)	0.532	2.11 (1.20-3.71)	***0.009***	1.01 (0.83-1.23)	0.900	1.02 (0.84-1.23)	0.877	1.23 (0.96-1.58)	0.101

analysis of data from the FACE-SZ cohort, which demonstrated an association between higher levels of inflammation with treatment with quetiapine, cyamemazine, and clomipramine, but not with olanzapine or clozapine (Fond et al., 2017). These antipsychotic-specific findings should be interpreted with caution in light of smaller sample sizes.

Key strengths of the present study include a large sample size and consideration of multiple potential confounding factors. Furthermore, the stability of CRP levels over long periods of time, coupled with the fact that CRP levels are unaffected by fasting status (Ridker, 2003), minimizes the likelihood that findings may have been affected by heterogeneity with respect to fasting status and timing of the blood draw. Limitations of the present study related to the patient sample include the varied clinical status of subjects (inpatient and outpatients), variable fasting status, and non-standardized antipsychotic treatment prior to entry into the CATIE trial.

Positive associations between inflammation and metabolic syndrome have been established by several studies in the general population (Kim et al., 2008; Lao et al., 2008; Ridker et al. 2008; Odagiri et al., 2011) and this may contribute to cardiovascular disease morbidity and mortality in patients with schizophrenia (Saha et al., 2007.; Mitchell et al., 2012; Mori et al., 2015). A growing body of evidence suggests that measurement and monitoring of inflammation markers may serve an important role in the management of patients with both schizophrenia and mood disorders, both in terms of likelihood of treatment response as well as adverse cardiometabolic risks. In a meta-analysis of 35 studies that assessed inflammation in depressed patients, Strawbridge et al. (2015) found that higher levels of baseline inflammation correlated with refractoriness to treatment. Similarly, in a longitudinal study of 68 patients, Mondelli et al. (2015) found that higher cortisol and inflammatory markers in patients with first-episode psychosis predicted worse treatment response. A mixed model analysis of depression symptoms and side-effect burden in patients in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial found that baseline CRP levels predicted a better response to combined SSRI and bupropion therapy than SSRI alone, and that low CRP levels predicted the inverse (Jha et al., 2017). Our finding that baseline inflammatory markers predicted incident metabolic syndrome, suggests that measurement of these markers may similarly be useful in guiding selection of antipsychotic therapy in the treatment of patients with schizophrenia. Furthermore, levels of these markers may serve a role in helping clinicians determine which patients are at higher risk for progression to metabolic syndrome, warranting closer surveillance of metabolic markers and/or prophylactic treatments to mitigate these risks (Mori et al., 2015).

Other recent studies have demonstrated associations between depression, antidepressant treatment, and metabolic disturbances in patients with schizophrenia. Major depressive disorder was associated with metabolic syndrome in patients with schizophrenia (Fond et al., 2018a, 2018b), and those with baseline depressive symptoms had a 4.5-fold higher risk of weight gain at one-year of follow up compare to patients without depressive symptoms (Godin et al., 2017). A cross-sectional analysis found that elevated CRP levels were associated with antidepressant use, but not with depression in schizophrenic patients, suggesting that studies investigating inflammation and schizophrenia should controlled for antidepressant treatment (Fond et al., 2016). Importantly, our findings remained significant after controlling for baseline use of antidepressants and/or mood stabilizers.

In conclusion, we found that baseline inflammatory markers, including CRP, IL-6, and leptin, predicted incident metabolic syndrome (and its components) in patients with chronic schizophrenia treated with antipsychotics for 12 months. These findings suggest that baseline levels of inflammatory markers may be useful to identify patients with schizophrenia at heightened risk for incident adverse cardiometabolic effects of antipsychotics. Given the tremendous burden of cardiovascular disease morbidity and mortality in schizophrenia, vigilant screening for and treatment of metabolic risk factors should be considered a high priority in clinical management in this patient population.

Conflict of interest

Mr. Kelly has nothing to disclose.

Dr. McEvoy has nothing to disclose for the work under consideration. In the past 12 months, Dr. McEvoy participated in Advisory Boards for Ameritox, Forum, Merck, and Otsuka; and has received research grants from Alkermes, Auspex, Avenir, and Otsuka.

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Contributors

Dr. Miller designed the study. Mr. Kelly and Dr. Miller managed the literature searches. Dr. Miller managed the analyses. Mr. Kelly and Dr. Miller wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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