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Individuals Hospitalized with Acute Mania Have Increased Exposure to Antimicrobial Medications

Robert Yolken¹, Maria Adamos², Emily Katsafanas², Sunil Khushalani², Andrea Origoni², Christina Savage², Lucy Schweinfurth², Cassie Stallings², Kevin Sweeney², and Faith Dickerson²

¹Stanley Neurovirology Laboratory, Johns Hopkins School of Medicine, Baltimore MD

²Stanley Research Program,, Sheppard Pratt Health System, Baltimore MD

Abstract

Objectives—We have previously documented that many individuals with acute mania have immune activation. However the sources of immune activation have not been identified. We investigated whether individuals hospitalized with acute mania have evidence of bacterial infections as determined by the prescription of systemic antimicrobial agents.

Methods—We assessed the recent prescription of systemic antimicrobial medications and the site of presumed bacterial infection in 234 individuals hospitalized for acute mania in either an inpatient unit or a day hospital. We also assessed individuals hospitalized for other psychiatric disorders (N=368) and controls (N=555). We employed logistic regression models to compare the rates of antibiotic prescription in individuals with the different diagnoses employing demographic variables as covariates.

Results—We found that individuals hospitalized with acute mania had a substantially increased rate of recent antimicrobial prescription defined as exposure within 3 days of ascertainment (Adjusted Odds Ratio 5.5, 95% CI 2.2, 14.1, $p < .0002$). Overall a total of 18 of the 234 (7.7%) of individuals hospitalized for acute mania were prescribed antibiotics as opposed to 7 of 555 (1.3%) controls. The prescription of antibiotics was associated with being in an inpatient unit as opposed to being in the day hospital and having increased mania symptom severity but not with other clinical ratings, demographic variables, or psychiatric medications. Hospitalization for other psychiatric disorders was not associated with the recent prescription of antimicrobial medications. The urinary tract was the most common site of infection in women while the respiratory tract and mucosal surfaces were the most common sites in men.

Conclusion—Individuals hospitalized with acute mania have a markedly increased rate of bacterial infections as evidenced by the recent prescription of antimicrobial agents. The prevention and effective treatment of bacterial infections may be important interventions for the management of individuals with mania.

Keywords

Infection; Mania; Inflammation; Antibiotic

Introduction

Mania is an abnormal mood state and the defining characteristic of bipolar disorder. Although genetic factors may play a major role in defining individual susceptibility to bipolar disorder, static factors such as genotype cannot be used to predict the episodic manic and depressive episodes that are the hallmark of this disorder. Immunological abnormalities have been identified that contribute to the pathophysiology of serious psychiatric disorders (1). Components of the immune system display altered levels in response to antigenic stimuli for a limited period of time and then can return to basal levels following the resolution of the immune reaction. Alterations in the immune system are thus plausible candidates for the episodic changes in behavior which are associated with mania. Several studies have documented immune activation in individuals undergoing episodes of acute mania (2). However, the origin of the immune activation in most individuals with mania has not been determined.

Exposure to microbial agents is recognized as one of the most common causes of immune activation in immune competent humans. Population-based studies have documented that bacterial infections can be a risk factor for the subsequent development of serious psychiatric disorders, including psychotic and mood disorders (3–5). Several of these studies employed the prescription of antibiotic agents as a measure of bacterial infections in target study populations. The focus on antibiotic prescription and utilization allows for the ascertainment of a wide range of different bacterial infections in diverse populations.

Previous studies of bacterial infections have focused on population-based cohorts and the use of registers for case ascertainment; there have been few studies of actively recruited and individually-ascertained populations with defined psychiatric disorders. Starting in 1999 we have enrolled and evaluated a large number of individuals with serious psychiatric disorders, including schizophrenia, bipolar disorder and major depression, as well as control individuals without a psychiatric disorder. Included in this cohort were individuals undergoing episodes of acute mania, bipolar depression, and major depression. Information obtained from these individuals included data relating to the administration of antibiotics and other medications around the time of hospitalization. Corresponding data were also collected from control individuals without a psychiatric disorder living in the same geographic region.

Methods

The study sample was drawn from the Stanley Research Program at Sheppard Pratt and included individuals enrolled in the program's studies in the period between February, 1999 and March, 2016 for a study of the association between infectious disease and immune markers and serious mental illness. The study populations were individuals who were

hospitalized with a diagnosis of mania, bipolar depression, major (unipolar) depression, or schizophrenia, as well as non-psychiatric outpatient controls.

Individuals with mania were recruited from inpatient and day hospital programs at Sheppard Pratt, an acute care psychiatric hospital located in Baltimore, MD. Inclusion criteria for the mania participants were: current admission to an inpatient or day hospital program for symptoms of mania or hypomania. Participants with mania could have an admission diagnosis of any one of the following: Bipolar I disorder, single manic episode; Bipolar I disorder, most recent episode manic; Bipolar I disorder, most recent episode mixed; Bipolar II disorder, most recent episode hypomanic; or Schizoaffective disorder, bipolar type (manic, hypomanic, or mixed state). Individuals with bipolar depression were recruited from persons admitted to an inpatient or day hospital unit at the same psychiatric hospital for symptoms of depression with an admission diagnosis of Bipolar I disorder, most recent episode depressed, or Bipolar II disorder, most recent episode depressed. Individuals with major depression were recruited from persons admitted to an inpatient or day hospital unit at the same psychiatric hospital for symptoms of depression with an admission diagnosis of major depression. Individuals with schizophrenia were recruited from persons admitted to an inpatient or day hospital unit with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Individuals without a history of psychiatric disorder were recruited from posted announcements at local health care facilities and universities in the same geographic area as the settings where the psychiatric participants were recruited. These control individuals were enrolled after they were screened to rule out the presence of a current or past psychiatric disorder with the Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition (6). Participants in all groups met the following additional criteria: age 18–65 (except the control participants who were aged 20–60); proficient in English; absence of any history of intravenous substance abuse; absence of mental retardation; absence of HIV infection; absence of serious medical disorder that would affect cognitive functioning; absence of a primary diagnosis of alcohol or substance use disorder. The diagnosis of each psychiatric participant was established by consensus of the research team based on the SCID for DSM-IV Axis I Disorders – Patient Edition (7) and available medical records.

For the purposes of this study, participants were only included in one psychiatric group with the order of selection: mania, bipolar depression, major depression, schizophrenia.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and the Johns Hopkins Medical Institutions following established guidelines. All participants provided written informed consent after the study procedures were explained.

At time of assessment, all participants were asked about receipt of all current medications. For psychiatric participants, medication data were recorded from the medical record within the previous 3 days. Medications were coded and classified as antibiotics for the purpose of this investigation if they were administered by the oral or parenteral route; antibiotics administered in the form of topical preparations or eye drops were not included.

For individuals with psychiatric disorders, the medical indication for the antibiotic was determined from the medical record. The record was also reviewed to determine when prescription of the antibiotic medication was started and if it was a continuation of medication received prior to hospital admission. In the control group the receipt of antibiotics within 3 days of assessment and the medical indication for the antibiotic medication were determined by an interview with the participant.

Participants were asked about their educational level and other demographic variables including maternal education as a proxy for pre-morbid socioeconomic status. All participants were individually administered a brief cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). All of the psychiatric participants were also interviewed and rated on the Brief Psychiatric Rating Scale (BPRS) (8–10) and the mood disorder participants on the Hamilton Depression Rating Scale and the bipolar disorder participants additionally on the Young Mania Rating Scale (11–12). Also for the psychiatric participants, psychiatric medication data were recorded from participant self-report and medical records and it was noted whether each patient was receiving each of the following types of medication within the 3 days prior to the study visit: atypical antipsychotic; lithium, non-lithium mood stabilizer, antidepressant medications.

Logistic regression models were employed to calculate the odds ratio associated with having been prescribed an antibiotic medication. Complete sets of data were available except for the Young Mania Rating Scale for which missing values were computed by imputation. These models were developed for each diagnostic group while adjusting for age, race (Caucasian vs. non-Caucasian), gender, highest level of education, level of maternal education, and current cigarette smoking (yes/no) as covariates. These factors were selected for inclusion as covariates since they have been associated with antibiotic usage in previous studies (13–15). Control individuals without a psychiatric disorder were used as the reference group for these analyses. Nested analyses were performed examining the subgroup within each psychiatric group who were in an inpatient unit at the time of assessment as opposed to individuals who were in a day hospital at the time of assessment employing the same covariates. Regression analyses within the group of individuals with mania were also performed to determine differences between individuals who were receiving antibiotics from those who were not, employing the same covariates as in the above analyses as well as symptom ratings scores and receipt of other medications

Results

The study sample consisted of a total of 1157 individuals including 234 hospitalized with acute mania, 101 with bipolar depression, 70 with major depression, 197 with schizophrenia, as well as 555 non-psychiatric controls. For the sample as a whole, the mean age was 33.2 (sd=12.8) years; 685 (59.2%) were female and 698 (60.3%) were Caucasian. A description of the demographic and clinical characteristics of each diagnostic group is shown in Table 1 and supplemental Table 1. A description of the care setting, scores on the Brief Psychiatric Rating Scale (BPRS), and psychiatric medications received by patients by the diagnostic group at time of study entry are presented in supplemental Table 2.

The rate of recent antibiotic prescription at the time of enrollment as defined by the prescription of systemic antibiotics is depicted in Table 1 and Supplemental Table 1. A total of 7 of the 555 (1.3%) of the control individuals were taking antibiotic medications at the time of enrollment. On the other hand, 18 of the 234 individuals hospitalized with mania (7.7%) were taking antibiotic medications at time of assessment. The rates of antibiotic usage for individuals hospitalized for schizophrenia, bipolar depression and major depression were 3.1%, 4.0%, and 2.9%, respectively.

We employed logistic regression models to calculate the odds ratio associated with recent antibiotic usage for each diagnostic group when adjusting for age, gender, race, highest level of education, maternal education, and cigarette smoking. As depicted in Figure 1, there were significantly increased odds of antibiotic usage in the mania group as compared to the controls (Adjusted Odds Ratio 5.5, 95% CI 2.2, 14.1, $p<.0002$). Elevated odds ratios of antibiotic usage were noted in some of the other diagnostic groups but these did not differ significantly from the controls ($p>.05$). Overall the rate of antibiotic usage in all psychiatric patients was increased over that of the controls (Adjusted Odds Ratio 3.7, 95% CI 1.5, 9.2 $p=.004$) Within the population of all psychiatric patients the rate of antibiotic usage did not differ between individuals who were inpatients as compared to those who were in the day hospital $p<.1$)

We also examined the rate of antibiotic usage in the subset of individuals who were inpatients (and not day hospital patients) at the time of assessment. As depicted in Figure 1 there was an even higher odds of antibiotic usage in the group of individuals with acute mania who were inpatients (Adjusted Odds Ratio 6.1, 95% CI 2.4,15.8, $p<00009$). The odds of antibiotic usage for the inpatients in the other diagnostic groups did not differ from that of controls ($p>.05$).

Data relating to antibiotic usage are depicted in Table 2 and Supplemental Table 1. Individuals in the study population with psychiatric disorders were receiving a wide range of antibiotic medications including ones of the tetracycline, penicillin, sulfonamide, cephalosporin, fluoroquinolone, and macrolide classes. All of the individuals were receiving their antibiotics by the oral route and all but one was receiving either a single antibiotic or a fixed antibiotic combination such as trimethoprim/sulfamethoxazole (sulfonamide class) or amoxicillin/clavulanate (penicillin class). There were no significant differences in terms of type of antibiotic by diagnostic group ($p>.1$).

The anatomical sites of infections necessitating antibiotic treatment are depicted in Table 3. Sites of infection that were identified included the urinary tract, respiratory tract, skin, soft tissue, and mouth. The distribution of sites of infection did not differ by diagnostic group ($p>.1$).

We also investigated antibiotic administration by gender (Table 4). There was not a difference in the overall rate of antibiotic usage between men and women ($\chi^2(2)=1.9$, $p<.1$). However, there were significant gender differences in the site of infection in the individuals with psychiatric disorders ($\chi^2(4)=16.1$, $p=.003$). Most of the difference was related to urinary tract infections which occurred only in women in the study population.

Within the group of individuals with mania, the identification of recent antibiotic usage did not correlate significantly with demographic variables such as age, gender, or race, receipt of specific psychiatric medications or psychiatric symptom severity as measured by the BPRS. However, as depicted in Table 5, individuals with mania who were receiving antibiotics had more severe mania symptoms at the time of assessment as measured by the Young Mania Rating Scale (Coefficient 5.04, 95% CI 0.45–9.6, $p=.032$, adjusted for age, gender, race, maternal education, educational status and cigarette smoking). Individuals who were or were not receiving antibiotics did not differ in terms of the receipt of psychiatric medications including lithium, anti-depressant, mood stabilizer, or atypical antipsychotic medications (all $p>.05$).

We attempted to determine the timing of antibiotic administration in the individuals with psychiatric disorders in relation to their admission to the inpatient unit or the day hospital. A total of 5 (16.7%) of the 30 individuals receiving antibiotics had been prescribed their antibiotic medications prior to admission while 12 (40%) of the individuals started their antibiotic course after admission. In the case of the remaining 13 (43.3%) individuals it could not be determined with certainty if they had been prescribed antibiotics prior to their hospitalization.

Discussion

Our data indicate that individuals undergoing an acute episode of mania at the time of their episode have an increased rate of recent antibiotic exposure compared to a control population. Some individuals hospitalized with other psychiatric disorders such as schizophrenia, bipolar depression, or major depression were also receiving antibiotics at the time of their hospitalization; however, the rates of antibiotic usage did not differ significantly from that of the control population.

Antibiotic usage could be related to a diagnosed bacterial infection in a number of different body sites. The most common types of infections were those of the urinary tract with all of the urinary tract infections occurring in women. This finding is consistent with previous studies (16) which describe increased rates of urinary tract infections in individuals with psychiatric disorders, particularly mood disorders. However, our study indicates that bacterial infections at other body sites are also associated with acute episodes of mania and other psychiatric disorders. Our findings also raise the question that antibiotic treatment may be a contributing factor to the association between urinary tract infections and psychiatric disorders.

There are several mechanisms by which antibiotic usage might be associated with episodes of acute mania. One possibility is that the underlying bacterial infections responsible for the antibiotic prescriptions result in immune activation which then leads to the onset of mania. This mechanism is consistent with previous studies documenting immunological disturbances in individuals undergoing episodes of acute mania (17–19). In such cases, the resolution of the bacterial infection may contribute to the decrease in the measures of immune activation which noted after the resolution of the mania episode (19). While the

mechanisms of immune activation in mania have not been conclusively determined, it is likely that epigenetic changes in the methylation may contribute to this process (20).

A second possibility is that the higher rate of presumed bacterial infections in individuals with mania is reflective of decreased levels of ability of the immune system to prevent infections in this population. This hypothesized mechanism is consistent with studies documenting decreased levels of innate immunity in individuals with mood disorders through inherited or acquired alterations in the activity of toll-like receptors, transcription factors, as expression of pentraxin proteins and other mechanisms (21–25).

A third possibility is that the administration of antibiotics can result in changes in the microbiome which themselves increased the risk of altered mood states (26). This finding is consistent with a number of studies in animal models linking the microbiome to altered behavior and cognition (27). However, the possible role of alterations in the microbiome in the onset of mania in our study population is rendered less likely by the fact that, in many cases, antibiotics were not administered to patients until after they had been admitted to the hospital. However, the possibility that the microbiomes may have been altered in these individuals by past administration of antibiotics cannot be excluded. It is of note that these proposed mechanisms of action are not mutually exclusive but might be interacting in different degrees to result in mania or other psychiatric symptoms in different individuals. Prospective cohort studies of antibiotic administration will be required to address these and other possible mechanisms linking antibiotic exposure and mood disorders.

There were a number of limitations to our study. These include a relatively small number of individuals documented to be receiving antibiotics and reliance on the medical record and participant interviews for clinical data. Studies with larger numbers of individuals and register based data infection and antibiotic prescriptions would be important in terms of confirming and extending our findings. In addition, larger samples sizes would allow for a more detailed analysis of sites of infection and the association with additional clinical rating scales such as ones related to psychosis and depression.

Our studies indicate that infections may be one of the instigating factors in some episodes of acute mania. Infections were also associated with other acute psychiatric conditions albeit at a lower level of statistical significance. Given our findings, it would be prudent for clinicians caring for individuals with a history mania to monitor them carefully for the occurrence of bacterial infections and to treat them promptly with an effective antibiotic.

These approaches should employ treatment with an appropriate antibiotic for a defined period of time to limit long-term effects of treatment on the microbiome (28). Approved methods for the prevention of infections, such as by the use of immunizations and prophylactic agents, should also be considered in individuals with psychiatric disorders. The control of bacterial infections in individuals with susceptibility to mania and other acute psychiatric conditions might result in the prevention of acute episodes and a marked improvement in their health and well-being.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Odds Ratios associated with receipt of antibiotics by diagnosis and hospitalization status as compared to the control group. Bars indicate mean and 95% confidence intervals of odds ratios adjusted for age, gender, race, educational level, maternal education, and cigarette smoking. Red bars indicate all hospitalized patients (day hospital and inpatient units) while blue bars indicated individuals hospitalized as inpatients. ** $p < 8.1 \times 10^{-5}$; * $p < 1.7 \times 10^{-4}$

Table 1

Characteristics of participants

	Controls N=555	Mania N=234	Bipolar Depression N=101	Major Depression N=70	Schizophrenia N=197
Mean Age (SD)	32.7 (11.4)	33.7 (13.0)	33.8 (12.7)	36.4 (12.6)	32.7 (13.5)
Gender-female	347 (62.5%)	151 (64.5%)	78 (77.2%)	39 (55.8%)	70 (35.5%)
Race - Caucasian	317 (57.1%)	168 (71.8%)	77 (76.2%)	46 (65.7%)	98 (49.8%)
Cigarette Smoker	97 (17.5%)	89 (38.0%)	37 (36.6%)	15 (21.4%)	100 (50.8%)
Receipt of systemic antibiotic ²	7 (1.3%)	18 (7.7%)	4 (4.0%)	2 (2.9%)	6 (3.1%)

Table 2

Types of antibiotics prescribed, by diagnostic group

Antibiotic type	Controls	Mania	Bipolar Depression	Major Depression	Schizophrenia
Tetracycline	2	3	0	0	2
Penicillin	2	5	2	2	1
Sulfonamide	0	6	2	0	1
Cephalosporin	0	2	0	0	1
Fluoroquinolone	1	1	0	0	1
Macrolide	1	1	0	0	0
Other/Unspecified	1	1	0	0	0
Total Antibiotics	7	19*	4	2	6

* One individual was receiving both a penicillin and sulfonamide antibiotic

Table 3

Site of infection, by diagnostic group

Infection site	Controls	Mania	Bipolar Depression	Major Depression	Schizophrenia
Urinary Tract	1	7	3	2	3
Skin/Soft Tissue	1	6	0	0	1
Respiratory Tract	2	2	0	0	0
Mouth/Teeth	1	3	1	0	1
Unspecified	2	0	0	0	1
Total Infections	7	18	4	2	6

Table 4

Site of infection in individuals with psychiatric disorders, by gender

Infection site	Case Men	Case Women	Control Men	Control Women
Urinary Tract	0	15	0	1
Skin/Soft Tissue	3	4	1	0
Respiratory Tract	2	0	0	2
Mouth/Teeth	3	2	0	1
Unspecified	1	0	1	1
Total Infections	9	21	2	5

Distribution of cases: $\chi^2(4)=16.1$, $p=0.003$

Table 5

Characteristics of Individuals with Mania Who Do and Do Not Have Evidence of Bacterial Infection

	Bacterial Infection N=18	No Bacterial Infection N=216	Significance¹
Age, Years ²	29.0 (9.3)	34.0 (13.2)	NS
Gender-Female	11 (61.1%)	140 (64.8%)	NS
Race-Caucasian	14 (77.8%)	146 (67.6%)	NS
Maternal Education-Years ²	13.7 (2.4)	13.8 (2.9)	NS
Educational Level-Years ²	13.0 (1.6)	14.0 (2.4)	NS
Cigarette Smoker	8 (44.4%)	81 (37.5%)	NS
Young Mania Rating Scale, total score ²	20.5 (9.5)	16.9 (8.8)	p<.032*
Brief Psychiatric Rating Scale (BPRS), total score ²	51.5 (10.1)	48.6 (8.7)	NS

¹ Adjusted for age, gender, race, educational level, maternal education, and cigarette smoking² Numbers indicate mean (standard deviation)