# Co-occurrence of Serious or Undiagnosed Medical Conditions With Bipolar Disorder Preventing Clinical Trial Randomization: A Case Series

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**ABSTRACT**

***Objective:*** Studies have shown that patients with bipolar disorder have high rates of serious and/or untreated co-occurring general medical conditions. This case series examined reports of co-occurring medical conditions with bipolar disorder in potential clinical study participants, and in particular the percentage of these individuals who were previously unaware of their conditions.

***Method:*** Patients were potential participants in 1 of 2 medication trials who met *DSM-IV* criteria for bipolar disorder and were excluded from those studies just prior to randomization from May 2009 through July 2011. Patients were compared with each other on a number of demographic criteria, including age, race, gender, reason for exclusion from the trial, and psychiatric diagnoses.

***Results:*** Of the patients excluded from the studies just prior to randomization, 31% (n = 10) were excluded because of medical conditions previously unreported by the patient during screening for these studies. Seventy percent of those excluded patients (n = 7) had no prior knowledge of their conditions.

***Conclusions:*** These results suggest that patients with bipolar disorder may not only have high rates of co-occurring medical conditions but also frequently remain unaware of those conditions. These findings indicate that co-occurring general medical conditions may be a more serious problem in the treatment of bipolar disorder than previously appreciated and that more stringent monitoring and guidelines are needed regardless of medication regimen. This case series asserts that, regardless of a patient's claim of having no medical conditions, more general medical screening may be needed in outpatient psychiatric settings.

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Patients with bipolar disorder have been found in a number of studies to have high rates of serious and/or untreated co-occurring general medical conditions.[1–3] These medical problems have serious negative effects in different areas of the patients' lives. Co-occurrence of medical conditions has been shown to have a detrimental effect on the success of psychiatric treatments across several different studies.[4–6] Co-occurring medical conditions in patients with psychiatric conditions have been linked to a decrease in lifespan of up to 25 years[7]; in particular, bipolar disorder is tied to higher mortality rates due to medical problems.[3,8] In patients with bipolar disorder, co-occurring medical conditions have also been linked to a lower quality of life at any age.[9]

A partial explanation for these high rates of untreated medical conditions could be that some patients with bipolar disorder engage in unhealthy lifestyles more than patients without mental illnesses; for example, patients with bipolar disorder are more likely to smoke or engage in substance abuse.[7] Additionally, childhood adversity, which has been found to have a negative impact on the onset and course of bipolar disorder,[10] has been linked to higher rates of medical condition co-occurrence with mental illness,[11] and this may also contribute to the high co-occurrence of medical conditions seen in bipolar disorder. Furthermore, there is evidence that second-generation antipsychotic medications, which are often used to treat bipolar disorder, are in some cases associated with higher rates of co-occurring medical conditions.[12]

This case series examines the phenomenon of high co-occurrence of medical conditions with bipolar disorder in 2 ongoing studies. A number of patients who otherwise qualified to participate in one of the studies were ruled out after having consented, just prior to randomization, because of the discovery of a medical condition that had not been reported in the extensive participant screening process up to that point. This article examines the rates of medical condition co-occurrence in potential participants in the 2 studies, as well as whether those subjects were aware of their condition before it was discovered during the screening process, and discusses the implications of these findings in light of previous findings regarding the frequency and consequences of the co-occurrence of bipolar disorder and untreated medical conditions.

## METHOD

This case series examined 2 ongoing randomized double-blind placebo-controlled drug trials. The first study, hereafter referred to as the *Depression study*, compares the use of lithium and sertraline in the treatment of patients with bipolar II depression who are currently in a depressive episode (funded by National Institute of Mental Health R01 collaborative grant MH074928; ClinicalTrials.gov identifier: NCT00276965). The second study, hereafter referred to as the *Anxiety study*, investigates the use of ziprasidone in the treatment of bipolar disorder with concurrent anxiety symptoms (funded by Pfizer Inc grant WS495334; ClinicalTrials.gov identifier: NCT01172652).

**Clinical Points**

- Patients with bipolar disorder often have co-occurring general medical conditions.
- Research suggests that these patients may frequently be unaware of their conditions.
- Clinicians can better treat patients with bipolar disorder by carefully screening for other medical conditions even when a patient does not report any.

In both trials, incoming participants undergo a 3-part screening process before randomization in the study, consisting of a phone screen, a new-intake visit, and a screening visit. The phone screens are designed to determine whether potential participants meet any major exclusions that would prevent them from being eligible for the studies. Common exclusions that are screened for include having no bipolar disorder diagnosis, an active or unstable medical condition, recent substance abuse or dependence, and recent hospitalization or active suicidality.

Participants who appear to be eligible after the phone screen are scheduled for a new-intake visit. During this visit, potential participants undergo a psychiatric evaluation by a psychiatrist or psychiatric nurse practitioner, after which the doctor confirms the individual's diagnosis and eligibility to participate in the study, including a verbal confirmation that the subject has no untreated or unstable medical conditions. Subjects are then given consent forms explaining the nature of the experimental procedures, approved by the Stanford University Institutional Review Board (IRB), which they are instructed to read and consider with their family.

If a subject decides to participate in one of the studies, a screening visit is scheduled during which he or she signs the informed consent form. The screening visit occurs after the consent form is signed, and it involves a full diagnostic interview and physical examination. Patients' mental states are evaluated using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID)[13] and standard clinical symptom scales. Patients also undergo a full physical examination. Included in this examination are an electrocardiogram, a urinalysis, a urine drug screen, and bloodwork including a thyrotropin panel, lipid panel, liver function test, hemoglobin $A_{1c}$ test, and γ-glutamyltransferase, as well as a complete blood count with differential and a comprehensive metabolic panel. Any patient with medical findings that the principal investigator rules to be indicative of an unstable medical condition, in the sense of being either not well controlled or potentially actively problematic, is excluded from the study.

All human subjects research performed in these studies was conducted in compliance with the Code of Ethics of the World Medical Association and the standards established by the IRB at the Stanford University School of Medicine. All subjects were fully informed of their rights, given ample time to review the consent form, and given the opportunity to ask any questions about the research with study personnel.

### Participants

The sample included participants recruited from May 2009 through July 2011 who had passed the phone screen and new-intake visit, signed the informed consent form, and participated in a screening visit (Figure 1). Seventy-eight total subjects were screened for the 2 studies combined, and they ranged in age from 19 to 64 years (mean = 41 years, SD = 12.45). The sample was evenly split by gender, consisting of 38 men and 40 women, and was predominantly white (69%, n = 54). Sixty-one subjects were screened for the Depression study, ranging in age from 22 to 64 years (mean = 41 years, SD = 12.57). The sample included 31 men and 30 women and was also predominantly white (66%, n = 40). For the Anxiety study, 17 subjects were screened, ranging in age from 19 to 53 years (mean = 35 years, SD = 10.81). The sample included 7 men and 10 women and had a majority of white volunteers (82%, n = 14). Patients were recruited from the community; participation in these studies was not limited to veterans.

Participants were divided into screen-failures (participants who gave consent to participate in the study but were never randomized) and randomized subjects (participants who were successfully screened and were included in the study). Screen-failures who were excluded from the study because of an unstable, untreated, or severe medical condition that was found after the individual signed the informed consent sheet were designated as medical-failures. Patients who were excluded for medical reasons at this stage were compared for age, race, gender, medical condition that led to exclusion from the study, psychiatric diagnoses, whether or not those diagnoses were confirmed by a full SCID, and nonstudy medications that the subjects were taking.

## RESULTS

For the 2 studies combined, a total of 32 patients gave consent to participate but were not randomized (designated as screen-failures). The screen-failures had a mean age of 39 years, ranging in age from 22 to 64 years (SD = 10.97), and were, like the sample of total screened participants, predominantly white (59.4%, n = 19) and nearly evenly divided by gender (43.75% female [n = 14], 56.25% male [n = 18]).

Of those screen-failures, 10 (31.3%) were excluded for medical reasons (designated as medical-failures). From the Depression study, 7 of the 25 screen-failures (28.0%) were excluded for medical reasons. From the Anxiety study, 3 of the 7 screen-failures (42.8%) were excluded for medical reasons (medical-failures). There were few meaningful correlations between the demographic data collected and the probability that a subject would be a medical-failure. The sample of medical-failures, like the sample of all screen-failures, was nearly evenly divided by gender (60.0% female [n = 6], 40.0% male [n = 4]) and ranged in age from 23 to 56 years, with a mean age of 40 years (SD = 10.22), comparable to the mean age of total screen-failures. The sample of participants who were medical-failures was mostly white (80.0%, n = 8), a higher percentage than in the sample of all screen-failures (59.4%, n = 19).

**Figure 1. Participants Screened in the Depression and Anxiety Studies**

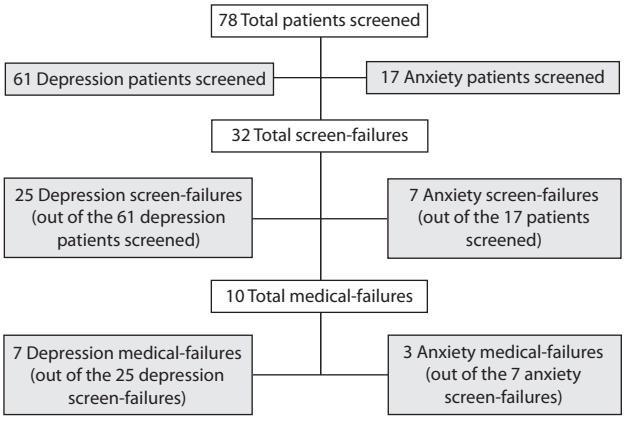


**Table 1. Characteristics of Medical-Failures From the Depression and Anxiety Studies**

| Patient Age (y) | Gender | Reason for Medical-Failure | Prior Knowledge of Condition? |
|---|---|---|---|
| Depression study | | | |
| 28 | Male | Hypokalemia | No |
| 43 | Female | Hypertension | Yes |
| 41 | Male | Hypertriglyceridemia (fasting triglycerides > 700 mg/dL) | No |
| 53 | Female | Hypertension | No |
| 56 | Female | Hypothyroidism | Yes |
| 23 | Female | Leukopenia | No |
| 38 | Female | Previously undiagnosed diabetes (fasting glucose > 200 mg/dL) | No |
| Anxiety study | | | |
| 40 | Female | Abnormal ECG | No |
| 37 | Male | Abnormal ECG (possible myocardial infarction) | No |
| 48 | Male | Untreated diabetes and hepatitis C (fasting glucose > 250 mg/dL) | Yes |

Abbreviation: ECG = electrocardiogram.

A pattern emerged in the co-occurrence of SCID-diagnosed Axis I psychiatric diagnoses between the 2 studies. Medical-failures from the Anxiety study had more co-occurring Axis I disorders than medical-failures from the Depression study; medical-failures from the Depression study had between 0 and 4 Axis I disorders co-occurring with their bipolar disorder (mean = 1.0), while medical-failures from the Anxiety study had between 2 and 6 co-occurring Axis I disorders (mean = 4.3).

Seventy percent of the medical-failures (n = 7) were unaware of the medical condition in question before it was diagnosed during the screening process. The most common conditions found in these patients were cardiovascular risk indications (n = 5), including hypertension, elevated triglycerides, and abnormal electrocardiogram findings, and endocrinologic abnormalities (n = 3), including untreated diabetes and hypothyroidism (Table 1).

The most common reasons that screen-failures who were not also medical-failures did not continue into the study were significant manic symptoms (n = 3) and a SCID diagnosis of "no bipolar disorder" (n = 3) of the 25 screen-failures in the Depression study (12.0% each) and withdrawn consent (n = 2) of the 7 screen-failures in the Anxiety study (28.6%). One subject signed a consent form for and then was excluded from both studies, for different reasons in each (an exclusion criterion for the Depression study was found earlier in the screening process than the relevant exclusion criterion found in that subject for the Anxiety study).

## DISCUSSION

This case series supports past findings that patients with bipolar disorder have high rates of serious or untreated medical conditions[1–3] and suggests an additional, disturbing trend: many patients with bipolar disorder are unaware of their general medical conditions. Before giving informed consent to participate in a study, patients underwent 2 levels of screening, both of which were intended, among other things, to exclude patients with medical problems. Those earlier levels of screening used self-report to determine which patients had medical problems; thus, any patients who had passed both of those screening phases would very likely have been unaware of any medical problems (because any patients aware of such problems would have reported them in the first 2 phases of screening and would have been excluded). However, a surprising number of patients who were considered fit to participate in one of these studies after 2 rounds of evaluation were discovered to have a medical problem that prevented them from doing so. This suggests that a high percentage of patients with bipolar disorder not only have co-occurring medical problems, but also are unaware of them.

It should be noted that participants from the Anxiety study had higher rates of both having co-occurring Axis I disorders and being excluded for medical reasons than participants from the Depression study (42.8% [n = 3] compared to 28.0% [n = 7], respectively). The sample size of patients involved with the Anxiety study is small. The finding of both higher rates of co-occurring Axis I disorders and greater need for treatment of medical problems is consistent with other studies.[14,15]

### Limitations

To pass the first 2 screening phases, patients had to confirm that, to their knowledge, they had no untreated or unstable medical problems. Because of this, patients designated as medical-failures would necessarily have been likely to be unaware of those medical conditions, since patients who were aware of any medical problems would quite likely have reported them and been excluded during the first 2 phases of screening. Thus, it is possible that the percentage of medical-failures who were unaware of their medical conditions (70.0%, n = 7) is higher in this sample than it might be in the general population. However, the presence of a high number of medical-failures after multiple levels of screening suggests that many patients with both bipolar disorder and


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medical problems may be unaware of their medical problems, and further study is warranted.

Additionally, the sample size in this case series is too small to draw statistically significant conclusions. However, this series does support past findings[1–3] and points to important trends that should be considered in the research and treatment of bipolar disorder. The small sample size also may have contributed to the lack of any clear trend in the specific medical conditions that medical-failures possessed. Future studies should investigate which specific medical conditions are more common reasons for exclusion from bipolar disorder studies.[16]

### Implications

The finding that patients with bipolar disorder are likely to have co-occurring general medical conditions is strongly supported by the existing literature.[1–3] The finding that these patients may not be aware of their conditions, however, is novel. Since past research has also shown that medical problems can cause serious detriment to patients with bipolar disorder, including higher mortality rates[3,8] and a lower quality of life at any age,[9] our findings suggest that undiagnosed or unreported medical problems in patients with bipolar disorder may have a larger effect than previously realized on the treatment of those patients.

These findings suggest a need for more diligent monitoring of patients with bipolar disorder in outpatient settings. The high risk of co-occurring medical conditions in patients with bipolar disorder is acknowledged in current treatment guidelines such as those of the International Society for Bipolar Disorders (ISBD) and Canadian Network for Mood and Anxiety Treatments (CANMAT)[17] and the Departments of Defense and Veterans Affairs.[18] However, neither set of guidelines contains sufficient recommendations for monitoring and addressing patients' medical conditions except as due to possible side effects from medication treatments. The ISBD/CANMAT guidelines explicitly state that monitoring of these conditions needs to be improved generally.[17] In light of the high rates of previously undiagnosed co-occurring medical conditions observed in even this small sample, it is important that future guidelines provide more stringent rules for monitoring patients' medical conditions, even in patients who do not report any medical problems.

## CONCLUSION

The findings of this case series suggest not only that patients with bipolar disorder may have high rates of co-occurring medical conditions, as has been previously found, but also that many of these patients may be unaware of their medical conditions and thus unable to report them when entering outpatient treatment. In light of the high rates of previously undiagnosed co-occurring medical conditions seen in this sample, regardless of current or past medication use, it is important that future guidelines address these issues explicitly.

***Drug names:*** lithium (Lithobid and others), sertraline (Zoloft and others), ziprasidone (Geodon).

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