Distinguishing between major depressive disorder and bipolar disorders has important clinical and public health implications. Although antidepressants are the cornerstone of treatment for major depressive disorder, this is not the case for bipolar depression, with additional concern that antidepressant treatment may destabilize mood and increase depressive episodes for some patients. Yet without biological validation to confirm the clinical diagnosis, accurate identification and differentiation of mood disorders sometimes can be challenging.

Because preliminary research has highlighted the potential usefulness of multiplex biomarkers, Mayo Clinic researchers undertook a feasibility study to determine whether high-throughput multiplexed immunoassay technology could be used to differentiate unipolar from bipolar depression.

"Unlike the evidence base in other fields of medicine, psychiatry doesn't have a blood test or brain scan to confirm a clinical diagnosis of a mood disorder. However, we know that biochemical dysregulation occurs with depression, and we wanted to see if this technology could ascertain differences and nuances in different types of depression,” explains Mark A. Frye, M.D., a psychiatrist at Mayo Clinic’s campus in Rochester, Minnesota, and lead study author.

In all, 288 volunteers were enrolled in the study — 46 with diagnosed bipolar I depression, 49 with bipolar II depression, 52 with unipolar depression and 141 controls. Serum samples were drawn from each participant and profiled for 320 proteins using Myriad RBM’s Multi-Analyte Profile platform. The platform originally was developed for immune and cytokine quantification for drug development; these same inflammatory and immune-mediated biomarkers are increasingly recognized in the underlying neurobiology of mood disorders.

"After correcting for multiple testing and adjusting for a number of clinical variables, six proteins showed statistically significant differences among the four groups (Figure). Those proteins included growth differentiation factor-15 (GDF-15), hemopexin (HPX),

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**Figure.** Comparison of protein levels among groups (BP-I = 46, BP-II = 49, UP = 52, controls = 141). All six protein levels were higher in BP-I vs. all other compared groups and controls. Five proteins were significantly different in BP-I vs. controls: GDF-15 P = 0.0278, HPX P = 0.0221, HPN P = 0.0156, RBP-4 P = 0.0001 and TTR P = 0.0012. BP, bipolar depression; GDF-15, growth differentiation factor-15; HPN, hepsin; HPX, hemopexin; MMP-7, matrix metalloproteinase-7; RBP-4, retinol-binding protein 4; TTR, transthyretin; UP, unipolar depression. Graphic reprinted with permission from *Translational Psychiatry.*
In 2010, a University of Washington study in the New England Journal of Medicine described a collaborative care model that improved outcomes and quality of life for patients with depression and coexisting diabetes or cardiovascular disease. The landmark study added to a growing body of evidence that such care models can significantly benefit people with chronic mental and physical conditions while holding the line on costs or even reducing them.

Despite this, collaborative care management is rare in primary medicine. To determine whether integrative care could be successful across varied settings, a consortium of 10 organizations developed the Care of Mental, Physical and Substance Use Syndromes (COMPASS) model. Initiated in 2012, COMPASS aims to improve the quality, experience and affordability of care for community-dwelling adults who have depression and chronic comorbidities — a population with disproportionately high health care costs and an increased risk of complications and premature death.

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“COMPASS is a national implementation and dissemination project that takes a model shown to work in research to see if it works on a larger scale,” explains David J. Katzelnick, M.D., a psychiatrist at Mayo Clinic’s campus in Rochester, Minnesota.

Eighteen medical groups are involved in COMPASS nationwide, including Mayo Clinic Health System locations in Minnesota and Florida. All target patients who have depression plus heart disease or diabetes. Many of these patients see a primary care provider, but only about half are diagnosed with depression and only half of those receive treatment. Most who are treated don’t experience much improvement.

“We know that comorbid psychiatric problems play a big role in patient complexity and prevent patients from getting better medically. In the COMPASS model, psychiatry and medicine join forces to deliver improved care for both mental and physical diseases simultaneously,” Dr. Katzelnick says.

**How COMPASS works**

COMPASS draws on the best practices of several collaborative care models, including Wagner’s Chronic Care Model, the Depression Improvement Across Minnesota, Offering a New Direction (DIAMOND) program and TEAMcare. Key components of COMPASS include:

- A care coordinator, usually a registered nurse, who meets with patients weekly to monitor their condition and provide support and active follow-up
- A consulting psychiatrist and primary care provider who review problem cases with the care coordinator on a weekly basis and make treatment recommendations to the primary physician
- A computerized registry, ongoing data analysis and quality improvement

“The critical component is the systematic case review, when the psychiatrist, care coordinator and physician expert work together to identify patients who aren’t doing well and need more attention,” Dr. Katzelnick says.

**For more information**

In the late 1970s, benzodiazepines were among the most commonly prescribed drugs in the world. Today, they continue to be one of the most frequently prescribed classes of medications for patients with bipolar disorders. Evidence exists to support their use in bipolar patients in acute settings as adjuncts to core mood stabilizers for improving sleep and controlling mania or agitated and aggressive behavior. But there is less evidence supporting their adjunctive use in long-term treatment.

William V. Bobo, M.D., a psychiatrist specializing in the evaluation and treatment of depression at Mayo Clinic’s campus in Rochester, Minnesota, says long-term benzodiazepine therapy in patients with bipolar disorder raises important safety concerns because of the potential for benzodiazepine abuse and the high prevalence of alcohol and substance use disorders in this population. Benzodiazepines may also be associated with a higher risk of mood episode recurrence.

“The concerning aspects of benzodiazepines create a dilemma for clinicians attempting to manage bipolar disorder — and coexisting anxiety disorders — over the long term,” he says. “In addition, outpatient doctors often inherit patients discharged from the hospital on benzodiazepines, and there is no clear evidence to guide decisions about continuing or stopping these drugs.”

To shed some light on the controversy, Dr. Bobo and colleagues looked at the effects of longer term adjunctive benzodiazepine therapy on core bipolar symptoms and associated anxiety and irritability using data from the Bipolar CHOICE study.

Bipolar CHOICE was a six-month randomized, multisite comparison of lithium and quetiapine-based treatment. Of the 482 patients

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**Longer Term Adjunctive Benzodiazepines May Not Improve Outcomes in Bipolar Disorder**

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with bipolar I or II disorder enrolled in the trial, 138 (28.6 percent) were considered benzodiazepine users at baseline or follow-up. The researchers then compared clinical measures, including the Bipolar Inventory of Signs and Symptoms (BISS) and Clinical Global Impressions-Bipolar (CGI-BP) scale, in benzodiazepine users and nonusers. Although improvement was seen in both groups, benzodiazepine users experienced significantly less improvement in BISS total, BISS irritability and CGI-BP scores than nonusers did. Benzodiazepine use also did not affect any outcome measure in patients with comorbid anxiety or substance use disorders. Results of the study were published in 2014 in the Journal of Affective Disorders.

“What we found is that adjunctive benzodiazepine use may not significantly affect outcomes in patients with bipolar disorders over the long term,” Dr. Bobo says. “We think this is an important finding given how frequently these drugs are prescribed for long periods and their potential for abuse and association with recurrences. The limitation is that this is only a secondary analysis of data from a trial not intended to address benzodiazepine use. Still, we think further study is warranted.”

In a second study using Bipolar CHOICE data, the same research team looked at the characteristics of patients who were prescribed adjunctive benzodiazepines. They found that users were more likely to have bipolar I disorder with comorbid anxiety, had experienced more anxiety, depressive symptoms and suicidality, and were prescribed significantly more psychotropic medications than nonusers were. Having a comorbid substance use disorder did not seem to affect whether patients were benzodiazepine users. Results of the study were published in 2015 in the Journal of Clinical Pharmacology.

“Higher illness complexity appeared to be the major driver of benzodiazepine use in patients with bipolar I and II disorder, and using benzodiazepines with more established treatments may represent clinicians’ best efforts to bring complex psychiatric symptoms under better control,” Dr. Bobo says. “But that has to be weighed against the risks and limited evidence supporting long-term benzodiazepine treatment. My recommendation would be to exercise caution. Not every patient is guaranteed a worse or no outcome with these drugs, but we need to better understand for which patients they may be safe and effective.”

For more information
Bobo WV, et al. Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: Results from the Bipolar CHOICE trial. Journal of Affective Disorders. 2014;161:30.