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ABSTRACT & COMMENTARY

The Holy Grail of Diagnosing Depression: An Effective Blood Test

By Martin S. Lipsky, MD

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Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

SYNOPSIS: An objective, laboratory based diagnostic tool for depression would be extremely helpful to primary care physicians. This study using nine biomarkers holds promise that a blood test may be able to identify depressed patients among non-depressed primary care patients

SOURCE: Redei EE, et. al. Blood transcriptomic biomarkers in adult primary care patients with major depressive disorder undergoing cognitive behavioral therapy. *Transl Psychiatry* 2014;4,e442 published online September 2014.

Major depressive disorder (MDD) is a complex psychiatric disease affecting 6.7% of the U.S. population.[1] Currently, the diagnosis of depression is based on self-reported symptoms and the evaluation of a provider such as a primary care physician, psychiatrist, or psychologist. Unfortunately depressed patients often underreport symptoms or inadequately characterize them. In addition, there is often discordance among the commonly used depression scales. It is not surprising then that only about half of MDD patients are recognized and treated by their primary care physician.[2]

An objective blood test that could accurately identify MDD would be an important and useful tool. This study used nine RNA transcript blood markers previously identified in animal models of depression and subsequently tested in a pilot study that distinguished subjects with early-onset MDD from matched controls.[3] Redei and her research team explored whether these markers could distinguish patients with MDD from non-

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depressed patients and also used them to follow MDD patients treated with cognitive behavioral therapy (CBT).

The study included 32 patients ranging in age from 21 to 79 years, who were seen at a university primary care clinic and were diagnosed with MDD and undergoing CBT and compared them to 32 non-depressed (ND) patients in the same age range. The study excluded patients who had initiated antidepressant pharmacotherapy in the past 10 days and patients with other psychiatric illnesses, hearing or visual problems, substance or alcohol abuse, exhibited severe suicidality, or who were undergoing or planning to receive individual psychotherapy.

At baseline, the blood marker levels in the control group differed significantly from patients with MDD. After 18 weeks of CBT therapy (either face-to-face or by telephone) biomarkers were retested. Differences in the blood markers differentiated patients who responded to CBT and were no longer clinically depressed (based on clinical interview and self-report) from those patients who remained depressed. Based on their findings, the authors conclude that the blood levels of different transcript panels may identify the depressed from the non-depressed among primary care patients and potentially predict response and/or permanent monitoring of response to CBT.

■ COMMENTARY

Depression is a serious disease that is frequently underdiagnosed in the primary care setting. Having the ability to augment the clinical diagnosis of depression with a blood test would clearly be of value to the primary care practitioner. In addition, having the ability to document changes in biomarkers associated with depression would convince patients of the biologic nature of the illness and that MDD is not just a weakness of spirit. This test also holds the promise of objectively tracking improvement and may be useful for individualizing therapy to the patient.

While the possibility of having such a diagnostic tool as part of the primary care provider's tool box is enticing, this test is still a long way from being ready for prime time. As the authors note, the study has several limitations. First, the sample size was modest and there were only two samples for each MDD subject and only one ND sample. Second, it may be that the biomarkers would not have been stable over time in the ND sample. The results could also have been strengthened by measuring the markers at different time points to see if changes correlated with the improvement of mood. In addition to the small sample size, the study involved only one practice setting and it will be important to see if the results are similar in other non-university settings.

Despite significant limitations, these early findings seem promising. Clearly there will need to be future studies with larger populations and also with study groups that include other psychiatric illnesses. However, while normally I would not report a study like this, which is still quite a ways off from being widely useful, I felt this test has such potential usefulness that it should be on the "watch list" of primary care providers. I suspect that if these preliminary findings hold up biomarker testing for depression will be embraced by PCPs and enhance their ability to diagnose and target treatment for depression. ■

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ABSTRACT & COMMENTARY

Aspirin for the Prevention of Recurrent Venous Thromboembolism

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

Patients with unprovoked venous thromboembolism (VTE) are at high risk of recurrence after discontinuation of vitamin K antagonist (such as warfarin) therapy, with an approximately 10% risk of recurrence within the first year and 5% risk per year thereafter.[1-6] Extending treatment with warfarin or similar agents reduces the risk of recurrence while treatment continues,[1-7] but such therapy is, of course, associated with an increased risk of bleeding and the inconvenience of laboratory monitoring and dose adjustment.[8] Several studies have evaluated the efficacy of the new oral anticoagulants for the prevention of recurrent VTE as part of the initial or the extended treatment regimen, but these drugs still carry a risk of bleeding and are expensive.[9-14] Therefore, aspirin, as a low-cost and relatively safe drug, was recently evaluated in the Aspirin for the Prevention of Recurrent Venous Thromboembolism (WARFASA)[15] and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trials.[16] These trials demonstrated that aspirin reduced the risk of recurrent VTE, but they were not sufficiently powered to detect moderate treatment effects for particular outcomes or subgroups.

Simes and associates performed an analysis of the two trials[15-16] in order to more accurately estimate the effects of aspirin therapy overall, on individual outcomes, and in prespecified subgroups of patients.[17] The major bleeding rate was low for both the placebo group and for the aspirin-treated group, and aspirin was found to reduce VTE by 42% in the broad cross-section of patients with a first unprovoked VTE.

■ COMMENTARY

Fewer than 50% of the patients in the United States and around the world with unprovoked VTE are routinely treated with long-term anticoagulant therapy.[18–20] The prospectively planned analysis of the WARFASA and ASPIRE trials using individual patient data provides strong evidence that in patients with a prior unprovoked VTE, aspirin, after any initial anticoagulation therapy had been completed, was effective in reducing the rate of VTE recurrence. It has been estimated that there are 1 million patients worldwide with unprovoked VTE and that if they were to remain on aspirin therapy long term, 100,000 events might be prevented with only a minimal increase in bleeding. Besides being cost-effective, more importantly, aspirin therapy in this group of patients is medically effective and should be continued long term.

In summary, the prospective combined analysis of the WARFASA and ASPIRE trials provides clear evidence that long-term aspirin therapy reduces the risk of recurrent VTE events by approximately 40% and is both very safe and effective. Even though it does not reduce the rate of recurrent VTE as much as warfarin or the newer oral anticoagulants, among patients for whom these therapies are not considered appropriate or have been discontinued for any reason, aspirin therapy should be strongly considered. ■

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ABSTRACT & COMMENTARY

Probiotic Supplementation Reduces Upper Respiratory Tract Infections

By Donald Brown, ND

Managing Director, Natural Product Research Consultants, Seattle, WA

Dr. Brown reports he is a retained consultant for Nature's Way and Linnea. This article originally appeared in the September 2014 issue of *Integrative Medicine Alert*.

SOURCE: West NP, et al. Probiotic supplementation for respiratory and gastrointestinal illness symptoms in healthy physical active adults. *Clin Nutr* 2014;33:581-587.

This 150-day, randomized, double-blind, placebo controlled trial (RCT) with 465 healthy adult volunteers (mean age 37 years old) was designed to examine the effects of probiotics on the incidence of upper respiratory tract infections (URTI). Participants were assigned to one of three groups:
1. *Bifidobacterium animalis* subsp. *lactis* Bl-04 (2×10^9 cfu/day);
2. *Lactobacillus acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07 (5×10^9 cfu of each strain per day); or
3. Placebo.

Each preparation was delivered in a powder to be mixed into a cold beverage. At the end of

the study, participants taking the Bl-04 had an approximately 27% reduction in risk of URTI compared to the placebo group (P = 0.022). There was no significant difference in the number of URTIs between the NCFM/Bi-07 group and the placebo group (P = 0.15). Both probiotic supplement regimens were associated with a delay in time to a URTI of approximately 0.8 months compared to placebo.

The results of this trial continue to support the use of probiotics for the prevention of URTIs. They add to the positive findings of a 2011 Cochrane Review meta-analysis of 10 RCTs which concluded that probiotics were superior to placebo in reducing the incidence of acute URTIs in adults and children as well as reducing antibiotic use.[1] It's interesting to note that a similar trial with preschool age children (included in the meta-analysis above) found that the combination of *L. acidophilus* NCFM and Bi-07 was effective in reducing the incidence of URTIs.[2] It is hard to speculate why the combination was not as effective with adults. ■

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PHARMACOLOGY UPDATE

Pirfenidone Capsule (Esbriet®) and Nintedanib Capsules (Ofev®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved two drugs for the treatment of idiopathic pulmonary fibrosis (IPF). Pirfenidone is an antifibrotic agent and nintedanib is a tyrosine kinase inhibitor. Both products were approved on a fast-track priority review, with orphan status and breakthrough designation. Pirfenidone is marketed by InterMune as Esbriet and nintedanib as Ofev by Boehringer Ingelheim.

INDICATIONS

Both drugs are approved for the treatment of idiopathic pulmonary fibrosis.[1,2]

DOSAGE

Pirfendone — the recommended dose is three capsules (801 mg) three times daily with food.[1] The dose should be titrated according to the following schedule: one capsule three times a day the first 7 days, two capsules three times a day through day 14, and three capsules daily thereafter.

Pirfendone is available as 267 mg capsules.

Nintedanib — the recommended dose is 150 mg twice daily, approximately 12 hours apart with food.[2] To manage adverse events, the dose may be reduced to 100 mg, or dosing may be temporarily interrupted or even discontinued.

Nintedanib is available as 100 mg and 150 mg capsules.

Pirfenidone and nintedanib represent drugs with new mechanisms of action for the treatment of IFD.

POTENTIAL DISADVANTAGES

Common adverse events (% vs placebo) for pirfenidone are nausea (36% vs 16%), rash (30% vs 10%), abdominal pain (24% vs 15%), and dyspepsia (19% vs 7%). Common adverse events for nintedanib are diarrhea (62% vs 18%), nausea (24% vs 7%), and abdominal pain (15% vs 6%). Both drugs are associated with an increase in liver enzymes. Nintedanib is not recommended for patients with moderate or severe liver

impairment.[1,2] Pirfenidone is not recommended for severe liver impairment. Pirfenidone is associated with photosensitivity and rash while nintedanib is embryotoxic.

COMMENTS

The safety and efficacy of both pirfenidone and nintedanib were evaluated in subjects with clinically confirmed IPF. Other eligibility criteria were forced viral capacity (FVC) at 50% or more of predicted, and diffusion capacity of lung for carbon monoxide (DLCO) of at least 30% predicted.[1,2,3,4] At baseline, the pirfenidone subjects had a mean FVC % of predicted of approximately 68%, compared to 81% for the nintedanib subjects. DLCO % of predicted were approximately 44% and 47%, respectively. The primary efficacy endpoint was decline in FVC. However, this was measured differently between drugs. For pirfenidone, it was the proportion of subjects who had a decline of >/= 10% from baseline to week 52 in the percentage of predicted FVC or who had died. The nintedanib study measured the annual rate of decline in FVC. Pirfenidone was evaluated in three placebo-controlled studies: two showed positive results and the third showed no difference in decline of FVC.[1] For study one (ASCEND) (n = 555), 17% of those randomized to pirfenidone met the endpoint compared to 32% for placebo (47% reduction). Study two showed similar results. For nintedanib, efficacy and safety were evaluated in two Phase 3 placebo-controlled studies (n = 513, 548).[2,4] Rates of decline in FVC were -115 mL for study one and -114 mL for study two, compared to -240 and -207, respectively, for placebo. The differences vs. placebo were -125 (95% confidence interval [CI], 78-173) and -94 mL (95% CI, 45-143). It is difficult to compare cross studies to try to glean potential differences, but using the pirfenidone endpoint, the 10% decline in FVC for nintedanib was 28% vs 43% for placebo (35% reduction).[2] Based on the studies cited in the respective labels, no statistically significant differences in all-cause mortality were observed for either drug. However, when data were pooled from two Phase 3 studies, survival significantly favored pirfenidone.[3]

CLINICAL IMPLICATIONS

IPF is a chronic, progressive, and fatal lung disease characterized by a decline in lung function due to proliferation of fibrous tissue in the lungs. Previous treatment, with limited effectiveness, includes prednisone, azathioprine, and N-acetyl cysteine.[5] Pirfenidone and nintedanib are the first FDA-approved treatments for IDF. These drug are effective in slowing the progression of the disease as measured by the decline in FVC. It is not clear whether one drug offers any clear advantage over the other, although some difference may emerge with more clinical experience. The wholesale cost for pirfenidone is $7800 for 30 days and for nintedanib is $8000 for 30 days for both the 100 mg and 150 mg doses. ■

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Internal Medicine [ALERT]

Clinical Briefs

By Louis Kuritzky, MD

Does It Really Make a Difference What Weight-reduction Diet You Choose?

Source: Johnston BC, et al. Comparison of weight loss among named diet programs in overweight and obese adults: A meta-analysis. *JAMA* 2014;312:923-933.

Since two-thirds of American adults are currently overweight or obese, we would all like to be able to help patients choose the "best" diet. The list of choices and categories is lengthy, with vocal advocates for the Atkins diet, the Zone diet, South Beach diet, Jenny Craig, Ornish, etc. Of course, were any of these diets sufficiently effective and easily adopted so that they could gain widespread advocacy, we wouldn't be faced with such an obesity epidemic in the first place! So apparently there is no "simple answer." Among the choices we have, then, which one might be the best?

Johnston et al performed a meta-analysis of weight-loss trials (n = 48 trials and 7286 subjects), including the above-mentioned diets. Diets were categorized further as low-carbohydrate or low-fat.

Although there were measurable statistical differences between diets, they were of dubious clinical significance. For instance, at the 12-month follow-up, low-carbohydrate diets were associated with a mean weight reduction of 7.99 kg vs 7.27 kg on low fat diets. Within-group diet differences (e.g., comparing Atkins and Zone diets, both of which are categorized as low carbohydrate) favored the former, but these differences were also very small (< 2 kg at 6 months).

Because of the modest outcome differences between diets, the authors conclude that whatever diet the patient can best adhere to should be recommended. ■

Treatment of Depression with Botulinum Toxin

Source: Magid M, et al. Treatment of major depressive disorder using botulinum toxin A: A 24-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2014;75:837-844.

The need for additional treatments for depression stems from the observation that only a minority of patients achieve full remission on currently available antidepressant medications, each of which with its own adverse effect profile. In the 1963 musical "Bye Bye Birdie," Dick van Dyke sang the song "Put on a Happy Face" (words by Lee Adams, music by Charles Strouse) to Janet Leigh. Having followed Dick's advice, Janet undergoes a prompt and readily visible transformation of her energy and mood. Well, maybe there was some substance to that advice, as suggested by this clinical trial of botulinum toxin (B-TOX).

The "Facial Feedback Hypothesis" suggests that when one volitionally produces a particular facial expression (e.g., frowning, smiling), concordant emotions are experienced, perhaps through some CNS feedback mechanism. So, might elimination of frown muscle tone with B-TOX improve mood?

Magid et al randomized 30 patients with depression to B-TOX vs. placebo administered at baseline in the facial glabellar region frown musculature. Depression scores were measured over 24 weeks post-injection.

B-TOX was associated with a statistically significant reduction in depression scores, which persisted throughout the 24-week interval, even though the cosmetic effects upon the facial frown musculature dissipated by 12-16 weeks.

Reductions in depression scores on the Beck Depression Inventory were impressive: more than one-third of B-TOX recipients achieved at least a 50% reduction in depression scores.

B-TOX appears to be a prompt and effective treatment for depression. ■

So You Were a Compliant Patient and Did Your Colonoscopy and Had an Adenoma Removed. Did it Pay Off? Well, Maybe.

Source: Løberg M, et al. Long-term colorectal-cancer mortality after adenoma removal. *N Engl J Med* 2014;371:799-807.

Compared to other preventive health screening interventions, adherence to colonoscopy (COL) recommendations is substantially less than that of other interventions. The payoff of reduced risk of colon cancer (CCA) seems insufficient inducement to undergo the procedural preparation and intervention for many of our patients. Just how big is the pay off?

Løberg et al investigated the impact on CCA mortality of adenoma removal during COL screening. They compared the CCA mortality over a 14-year interval (median follow-up = 7.7 years) for persons who had undergone colonoscopic adenoma removal with the CCA mortality in the entire adult population of Norway. The primary outcome of the study was the rate of CCA mortality, as assessed by the Stratified Mortality Ratio (SMR): the rate of CCA deaths in persons with adenomas removed vs the CCA death rate in the general adult population.

Based on 383 CCA deaths among 40,826 adenoma patients, compared to 398 CCA deaths in the general population, the overall SMR (including all classes of adenomas excised) demonstrated a trend toward lower CCA mortality (SMR, 0.96; confidence interval, 0.87-1.06). ■

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CME QUESTIONS

1. **A new blood test that is being tested for depression that will be able to:**

   a. identify bipolar patients.

   b. predict which patients with major depression will respond to SSRIs.

   c. differentiate patients with major depressive disorder from non-depressed patients.

   d. identify depressed patients at risk for alcohol abuse.

2. **Long-term low-dose aspirin therapy given to patients with venous thromboembolism (VTE):**

   a. minimally reduces the overall risk of VTE recurrence.

   b. is associated with a significant risk of bleeding.

   c. reduces recurrent VTE by 42%.

   d. reduces the rate of recurrent VTE more than is achieved by warfarin or by the newer anticoagulant agents.

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