According to a systematic review and meta-analysis, preliminary evidence supports significant antidepressant effects of minocycline (Minocin) in patients with unipolar major depression.

**Background:** The immune system has been identified as a novel target in the treatment of depression, and replicated evidence clearly supports the strategy. Minocycline, a tetracycline antibiotic with potent antiinflammatory and neuroprotective effects, has been evaluated in several small controlled trials in both unipolar and bipolar depression. The present analysis was undertaken to synthesize these results.

**Methods:** A comprehensive literature search was performed to identify reports, including clinical trials, case reports, and observational studies, of minocycline as a treatment for a major depressive episode in unipolar or bipolar depression. All identified studies were included in a qualitative review, and randomized controlled trials of minocycline—as either adjunctive treatment or monotherapy—were included in a meta-analysis. A total of 17 studies were identified: 3 published controlled trials; 2 open-label studies; 1 case report; 3 clinical trials that have been completed but have not yet been published; 1 study that was terminated for product supply issues; and 7 additional studies that are ongoing.

**Results:** Both open-label studies evaluated adjunctive minocycline (1 in unipolar and 1 in bipolar depression) and reported significant improvements in depression rating scale scores following 6–8 weeks of treatment (p<0.001 in bipolar depression and p<0.008 in unipolar depression). The single case report also described improved depression with adjunctive minocycline. Preliminary results were available online for 2 of the 3 unpublished studies. Both evaluated open-label treatment and reported 8–15-point reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores in treated patients. No serious adverse events were described in any of the reports.

The 3 randomized controlled trials comprised a total of 162 patients (52% women) with mean ages ranging from 35 to 51 years. All patients had a diagnosis of unipolar major depression, and...
minocycline was an adjunct to treatment as usual in 2 of the studies. In the pooled analysis, minocycline was significantly superior to placebo at reducing MADRS or Hamilton Rating Scale for Depression scores with a standardized mean difference* of -0.78 (p=0.005). Minocycline was well tolerated; adverse effects were similar to placebo, and none were serious.

**Discussion:** Although the number of studies and enrolled patients was small, the results of this meta-analysis do provide preliminary support for the efficacy of minocycline in patients with depression; the additional studies support these findings. Several larger-scale ongoing trials evaluating minocycline efficacy in both unipolar and bipolar depression continue to recruit patients, and the full results of the completed but as-yet unpublished studies should help to clarify the robustness of minocycline efficacy and tolerability.

**Study Rating**—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, the source of funding was not included.

Rosenblat J, McIntyre R: Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *Journal of Affective Disorders* 2017; doi 10.1016/j.jad.2017.10.042. From the University of Toronto, Canada.

Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.

*See Reference Guide.

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**Pharmacogenetic-Guided Treatment**

In a randomized trial, pharmacogenetic-guided drug selection resulted in improved treatment efficacy in patients with depression and/or anxiety. The trial, funded by the manufacturer of the genetic test, is notable for including patients from both diagnostic categories and from both psychiatric and primary-care practices.

**Background:** The NeurolDgenetix® Test is based on a panel of 10 genes and accounts for concomitant medications, over-the-counter treatments, and lifestyle factors such as supplements, diet, alcohol, and smoking. The test results in recommendations based on gene/drug and drug/drug interactions for >40 medications used to treat depression and anxiety. The report classifies medications as either "use as directed" or "use with caution and/or increased monitoring," the latter including reasons for caution and recommendations for appropriate action.

**Methods:** Study participants were adults with DSM-5 unipolar depression and/or anxiety, enrolled from 20 U.S. clinical sites representing psychiatry, internal medicine, OB-GYN, and family practice. Patients were randomly assigned to the experimental group whose treatment was guided by NeurolDgenetix results or a control group receiving usual treatment. Before randomization, all patients had specimens collected (buccal swabs) for genetic testing, but physicians only received the results for patients in the experimental group. Patients returned for assessment at weeks 4, 8, and 12. Treatment outcomes were assessed by raters, unaware of patients' treatment assignment and therapeutic decisions made by the treating physician, using the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A). Response was defined as a ≥50% reduction in score, and remission as a final score of ≤7. Adverse drug events were also rated by a blinded observer. While the treating physicians could not be blinded to patient arm assignment, they were blind to symptom severity scores (raters categorized symptoms as either mild, moderate, or severe based on score cutoffs), thus ensuring that any expectancy bias did not affect clinical outcome measures.

**Results:** Of 685 patients enrolled, 579 (85%) completed the study. Patients had a mean age of 48 years, 73% were women, and 18% were African-American. The sample was about evenly divided among patients with depression alone, anxiety alone, and both diagnoses.

Patients with mild depression (i.e., HAM-D scores ≤17) did not improve with treatment, which is consistent with research suggesting medication is ineffective in mild depression. For patients
with severe depression (i.e., HAM-D scores >24), pharmacogenetic testing was associated with higher rates of response at 12 weeks: 73% vs 36% (p=0.001) with an odds ratio* (OR) of 4.72 favoring the pharmacogenetic-guided group and a number needed to treat* (NNT) of 2.7. When patients with moderate depression were included, results were attenuated but remained significant (p=0.01; OR, 2.03; NNT, 5.8). Results for remission in patients with severe depression showed a similar pattern: 35% vs 13% (p=0.02) with an OR of 3.54 and an NNT of 4.6. Remission rates in the group with moderate-to-severe depression were not reported.

Pharmacogenetic-guided treatment was also associated with significantly better outcomes in patients with anxiety. At 12 weeks, HAM-A reductions were 54% in the experimental group and 42% in the control group (p=0.02). Response rates were 63% and 50%, respectively (p=0.04; OR, 1.76; NNT, 7.3). Patients with anxiety and comorbid depression also improved significantly, but to a lesser degree than patients with anxiety alone.

Physicians implemented or modified therapy during the trial in more patients in the experimental group than the control group (p<0.0001; overall percentages not reported). Most medication changes occurred at the 2-week visit (81% of the experimental group and 64% of controls), and changes continued throughout the study. Medication changes in the experimental group were aligned with recommendations 70% of the time. No differences in adverse event rates or severity were observed between groups, suggesting medication changes were not driven by adverse effects.

Discussion: These results support the use of pharmacogenetics to improve outcomes in depression and to a lesser extent, anxiety. While patients with both depression and anxiety also improved, the effects of pharmacogenetic testing in these patients were smaller; additional research is needed to examine this difference.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Bradley P, Shiekh M, Mehra V, Vrbicky K, et al: Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. Journal of Psychiatric Research 2017; doi:10.1016/j.jpsychires.2017.09.024. From Mercer University School of Medicine, Savannah, GA; and other institutions including AltheaDX, San Diego, CA. Funded by AltheaDX, manufacturer of the NeurolDgenetix® test. Five of 10 study authors disclosed financial relationships with AltheaDX; the remaining authors declared no competing interests.

*See Reference Guide.

Ramelteon for Agitation in Delirium

According to the results of a retrospective chart review, the melatonin receptor agonist ramelteon (Rozerem) is associated with reduced use of as-needed antipsychotics for agitation in elderly inpatients with delirium. This finding suggests that correcting circadian-rhythm disturbance may be a potential treatment for delirium.

Background: There is no drug FDA-approved to treat delirium. Antipsychotics are often prescribed, despite their risks and an FDA black box warning about mortality risk in elderly patients with dementia. Research has identified degeneration of the suprachiasmatic nucleus of the hypothalamus resulting in reduced melatonin secretion and disrupted circadian rhythm in patients with delirium.

Methods: Data from a single general hospital between May and October 2015 were analyzed retrospectively. The study sample included 125 patients (52% women), aged ≥65 years, who had a diagnosis of delirium, were on continuous observation, and had no standing orders for antipsychotics. Continuous observation included 1-on-1 observation for those experiencing suicidality or at risk of harming themselves or others, and safety watch for those with cognitive deficits or impaired judgment leading to agitation, risky actions, or falls.
Patients with underlying psychiatric disorders were excluded. In the 60 patients (48%) who received ramelteon treatment, the prescription had been based on the clinicians’ judgment that they would benefit from the regulation of circadian rhythm. As-needed antipsychotics were used to treat agitation, regardless of ramelteon use. The primary outcome of the analysis was use of as-needed antipsychotics.

**Results:** During their hospital stay, as-needed antipsychotics were used by 60% of the patients who received ramelteon, compared with 86% of those who did not (p=0.001). In a multivariate analysis adjusted for race, gender, age, and length of stay, patients who did not receive ramelteon had a significantly higher likelihood of receiving an antipsychotic (odds ratio,* 4.3; p=0.002). Among patients who received antipsychotics, the groups did not differ in the type of drug or the dosage. Average length of stay did not differ significantly between the groups.

**Discussion:** While these results suggest ramelteon may reduce use of as-needed antipsychotics, the study design precluded evaluation of potential confounders and selection bias could not be prevented. Further research with well-designed, prospective studies appears to be warranted.


From NYU Winthrop Hospital, Mineola; and St. John's University, Queens, NY. The study was conducted without funding. The authors declared no competing interests.

*See Reference Guide.

**Mood Stabilizers in Older Patients**

Lithium and divalproex had similar overall efficacy and tolerability in a 9-week randomized comparison trial in older patients with bipolar mania. Contrary to expectations, dosing was not limited by adverse effects to a greater extent with lithium than with divalproex.

**Background:** Lithium has the strongest evidence supporting its efficacy in adults with bipolar disorder. However, older patients may be unable to tolerate lithium at the concentrations recommended for younger patients, and concerns about tolerability may lead to use of lower doses or alternative medications, such as divalproex.

**Methods:** Study participants were recruited from 6 U.S. academic medical centers and included both inpatients and outpatients. For inclusion, patients were required to: be aged ≥60 years; meet DSM-IV criteria for bipolar 1 disorder with a current manic, mixed, or hypomanic episode; and have a Young Mania Rating Scale (YMRS) score of ≥18. Following taper and discontinuation of antidepressants and other non-study medications, patients were randomly assigned to 9 weeks of double-blind treatment with either lithium or divalproex. Lithium was initiated at 300 mg/day and titrated to a target serum concentration of 0.80–0.99 mEq/L. Divalproex was initiated at 500 mg/day and titrated to a target of 80–99 µg/mL. Participants who did not have an adequate response at week 3 were given adjunctive risperidone. Those who could not tolerate dosing that achieved the minimal serum targets were withdrawn. The study had 3 primary outcomes: clinical tolerability, measured using the UKU Side Effect Rating Scale sleepiness/sedation item; pharmacologic tolerability, which was the proportion of patients who achieved serum concentrations within the target range; and efficacy, measured as the change from baseline in the YMRS score.

**Results:** A total of 224 patients (mean age, 68 years; age at first onset of mania, 9–82 years) entered the study. Similar proportions of both groups did not complete 9 weeks of study treatment: 51% with lithium and 44% with divalproex. Reasons for attrition—nonadherence, intolerance, or lack of efficacy—did not differ between the groups. Similar proportions of the lithium and divalproex groups used adjunctive risperidone: 17% and 14%, respectively.
Levels of sleepiness/sedation, the primary tolerability outcome, rated at 3 and 9 weeks did not differ between the 2 drugs. Tremor occurred somewhat less often with divalproex, but the difference was not significant, and there were no significant differences in nausea/vomiting or weight gain. Similar proportions of patients in both groups achieved target drug concentrations: about one-third at week 3 and about 55% at week 9.

Significant differences between the 2 drugs in YMRS improvement, favoring lithium, were observed at week 3 (between group difference, 1.6 points; effect size,* 0.18) and week 9 (mean difference, 4 points; effect size, 0.54). Further analysis indicated that the difference in efficacy was limited to patients with a baseline YMRS score >30. The groups did not differ in rates of response, defined as a ≥50% reduction in YMRS total score: about two-thirds at week 3 and three-fourths at week 9. Remission (i.e., YMRS total score ≤9) occurred in nearly half of patients at week 3 and two-thirds at week 9. Neither agent was associated with worsening of depressive symptoms.

Discussion: Older patients appear to tolerate treatment with lithium or divalproex with conservative serum concentration targets, as well as limited use of rescue and adjunctive medication. Based on their findings, the authors recommend greater use of lithium, which may have neuroprotective and antisuicide effects. However, according to an accompanying editorial, the choice of an acute therapy should include considerations for maintenance therapy, and maintenance treatment with lithium in the elderly may be limited by a higher risk of long-term toxicity, particularly renal and cardiac effects.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.


2Dunner D: Treatment of bipolar disorder in the elderly [editorial]. American Journal of Psychiatry 2017;174 (November):1032–1033. From the Center for Anxiety and Depression, Mercer Island, WA; and the University of Washington, Seattle. The author disclosed financial relationships with commercial sources.

Common Drug Trade Names: divalproex sodium (valproic acid and derivatives)—Depakene, Depakote; risperidone—Risperdal

*See Reference Guide.

### Venlafaxine and Bone Turnover

In older patients with depression treated with venlafaxine (Effexor), antidepressant response appeared to protect against an increase in markers of bone resorption associated with SRI treatment.1 This observation suggests the possibility that when serotonergic antidepressants are ineffective in treating depression, a switch to a different class of antidepressant rather than augmenting the SRI may have favorable effects on bone turnover.

Background: Bone cells have functional serotonin receptors, and SRI therapy has been associated with accelerated bone loss and increased fracture risk in some studies of older patients. SRIs affect bone cells via the serotonin transporters and receptors. Results of a previous trial, conducted by several of the present study authors and at the same institutions, indicated that patients whose depression remitted with venlafaxine had minimal changes in bone turnover markers, suggesting successful antidepressant response may mitigate bone turnover.2 However, the study sample (n=73) was small. The present report pools those patients with an additional 95 to increase statistical power and to explore additional variables.

Methods: Participants in this open-label study of venlafaxine were aged ≥60 years and experiencing a major depressive episode, of at least moderate severity, for ≥4 weeks. Those receiving bisphosphonates were excluded, but other bone-protective treatments (vitamin D, calcium, and
estrogen), taken consistently throughout the study, were permitted. All participants received 12 weeks of treatment with venlafaxine, titrated to a target dosage of 150 mg/day. Those whose depression did not remit (i.e., Montgomery-Asberg Depression Rating Scale score of ≤10) after 6 weeks received a further titration to a maximum of 300 mg/day. Blood samples were obtained at baseline and 12 weeks and assayed for CTX, a marker of osteoclast activity and bone resorption, and P1NP, a marker of osteoblast activity and bone formation. Patients were also genotyped for numerous polymorphisms in the serotonin transporter (HTTLPR) and receptor (HTR1B) genes, which were grouped as having high or low activity.

Results: The 168 participants had a mean age of 69 years, 61% were women, and 92% were Caucasian. They were generally physically healthy and cognitively intact. A total of 80 patients (48%) experienced remission of depression. The mean venlafaxine dose at study end was about 200 mg/day in remitters and 268 mg/day in nonremitters.

Overall, the mean levels of CTX increased significantly in patients who received venlafaxine (p=0.02 for mean change from baseline), and levels of P1NP significantly decreased (p=0.01). CTX increased in 55% of the venlafaxine-treated patients, and P1NP decreased in 61%. The increase in CTX was significant in patients who did not achieve remission (p=0.009), while levels showed no change in those whose depression did remit. P1NP decreases occurred in both nonremitters and remitters. In a multivariable model controlling for baseline biomarker levels and other potentially confounding factors, remission status was correlated with end-of-treatment CTX levels (p=0.008), but not P1NP. Levels of P1NP were also lower in patients who had a depressive episode lasting >2 years.

Among Caucasian patients, 30% had a low-expressing serotonin receptor genotype and 29% a low-expressing serotonin transporter genotype. In the multivariable model, the receptor genotype predicted end-of-treatment P1NP (p=0.03), but not CTX. The serotonin transporter genotype was not associated with end-of-treatment levels in either marker.

Discussion: Although still preliminary, the present results support the hypothesis that accelerated bone loss in older individuals taking antidepressants is an effect of the drug, not of depression, and that it can be moderated by antidepressant response. Venlafaxine has binding affinity that is predominantly serotonergic, which suggests that the findings may be broadly applicable to serotonergic antidepressants in general; however, other individual agents should be evaluated. Regardless of the causation of the association, these results suggest that depression of long standing, treatment response, and serotonin receptor genotype may be useful in identifying patients at risk of accelerated bone loss.

Methods: The trial recruited patients from 5 urban addiction clinics in Norway. Participants met DSM-IV criteria for opioid dependence, but were not dependent on other drugs or alcohol and

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**Naltrexone for Opioid Dependence**

In a randomized trial, injectable extended-release naltrexone was as effective as daily oral buprenorphine–naloxone in the short-term treatment of opioid dependence. Buprenorphine–naloxone is among the most commonly prescribed opioid medication treatments but requires daily or alternate-day dosing. An important potential advantage of extended-release naltrexone is once-monthly injection.

Methods: The trial recruited patients from 5 urban addiction clinics in Norway. Participants met DSM-IV criteria for opioid dependence, but were not dependent on other drugs or alcohol and...
did not have other serious psychiatric illness. All participants received treatment as outpatients after discharge from detoxification units, inpatient treatment, or prison. Patients were randomly assigned to receive naltrexone injections (380 mg every 4 weeks) or flexible-dose, daily oral buprenorphine–naloxone, given in a controlled environment. Treatment was provided for 12 weeks. The primary outcomes were retention in the study, the number of weekly urine drug tests free of opioids, and the patient-reported number of days of use of heroin and other illicit opioids. Missing drug screens were considered to be positive for opioids.

**Results:** Of 232 patients assessed for the study, 51 refused to participate. After exclusions for other reasons, 159 (mean age, 36 years; 28% women) were randomized. Patients had an average of >6 years of heavy heroin use. Similar numbers of patients completed 12 weeks of treatment: 56 in the naltrexone group and 49 in the buprenorphine–naloxone group.

The treatments were similar with regard to the mean proportion of opioid-negative urine tests: 90% for naltrexone, 80% for buprenorphine–naloxone. Naltrexone was noninferior with regard to the mean number of days of heroin use (mean difference, 3.2 days) and days of use of other opioids (mean difference, 2.7 days). However, patients who received naltrexone used significantly less heroin at all 3 time points and significantly less other illicit opioids at weeks 4 and 8. At all time points, patients receiving naltrexone reported less craving and thoughts about heroin. They also had a higher level of satisfaction with treatment and were more likely to recommend it to others than those in the buprenorphine–naloxone group.

Adverse events related to opioid withdrawal—e.g., nausea, chills, and diarrhea—were more common in the naltrexone group (39% vs 14%). Insufficient detoxification appeared to be a factor, and the incidence of these adverse effects declined when the detoxification strategy for the study was strengthened.

**Discussion:** These results apply to illicit opioids but are likely clinically relevant for people addicted to prescribed opioids as well. The relatively high level of patient satisfaction with naltrexone may be related to the feeling of being protected against relapse and the freedom from having to attend supervised medication intake. Study participants were highly motivated to achieve opioid abstinence, and it is unknown whether extended-release naltrexone would be as effective in a less motivated population.

**Common Drug Trade Names:** buprenorphine–naloxone—Suboxone; naltrexone, injectable extended release—Vivitrol

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### Monthly Buprenorphine for Opioid Use Disorder

The Psychopharmacologic Drugs and Drug Safety and Risk Management Advisory Committees of the FDA have recommended approval of an investigational once-monthly sustained-release buprenorphine injection (RBP-6000) for the treatment of moderate-to-severe opioid use disorder.

The new buprenorphine formulation makes use of the Atrigel® delivery system, which consists of a biodegradable polymeric solution and a water-miscible biocompatible solvent. After subcutaneous injection, the solvent diffuses out of the polymer matrix and the polymer precipitates, trapping buprenorphine inside and forming a solid depot at the injection site. The depot then releases buprenorphine over a 1-month period by diffusion as the polymer biodegrades. In clinical trials, RBP-6000 produced significantly greater abstinence rates than
placebo, with a safety profile similar to that of oral transmucosal buprenorphine (Subutex). Injection-site reactions resulted in <1% of patients withdrawing from the trials.

While the recommendations of the FDA advisory committees are not binding, they do play a major role in the decision process. The FDA expects to take action on the decision by the end of November.


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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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