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Change Coming . . . See back page for details.

Quetiapine/Venlafaxine Interaction

Co-administration of quetiapine was associated with increased levels of the active metabolite of venlafaxine in an observational study. The increase in the venlafaxine metabolite and active moiety is moderate but clinically significant, possibly influencing antidepressant action and adverse effects.

Methods: The study was based on serum drug measurements from inpatients with various psychiatric disorders who received treatment at a single facility in 2013–2016. Trough blood samples were drawn before the morning dose during steady state drug administration. The database included 153 patients who received an oral formulation of venlafaxine alone and 71 who were co-medicated with quetiapine. The analysis excluded patients taking other drugs that influenced the relevant cytochrome P450 pathways. Samples were analyzed for levels of venlafaxine, the active metabolite *O*-desmethylvenlafaxine, and the active moiety (venlafaxine plus *O*-desmethylvenlafaxine).

Results: The 2 groups were similar in age and gender distribution and received a similar mean dosage of venlafaxine: 171 mg/day in the monotherapy group and 183 mg/day in the comedicated group. The mean dosage of quetiapine was 241 mg/day. Most patients (n=65) received extended-release quetiapine.

The group receiving quetiapine had significantly higher levels of *O*-desmethylvenlafaxine (265 ng/mL vs 205 ng/mL; p=0.003) and the active moiety (354 ng/mL vs 305 ng/mL; p=0.002) than the monotherapy group. Levels of venlafaxine were numerically but not statistically higher in comedicated patients (81 ng/mL vs 66 ng/mL). The ratio of the active metabolite to parent compound did not differ significantly between the 2 groups. Dose-adjusted levels of *O*-desmethylvenlafaxine and the active moiety were also elevated significantly in the comedicated group (p=0.015 and p=0.038, respectively).

Discussion: Venlafaxine and quetiapine partially share the same metabolic pathway, which influences metabolism of *O*-desmethylvenlafaxine but not the major inactive venlafaxine

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metabolite, *N*-desmethylvenlafaxine. In the present analysis, comedication was associated with a 29.3% increase in levels of *O*-desmethylvenlafaxine and a 15.8% increase in the active moiety, indicating reduced venlafaxine clearance. The authors note that CYP2D6 genotype, which could affect venlafaxine metabolism, was not evaluated in the study patients, possibly limiting the generalizability of the findings.

Paulzen M, Schoretsanitis G, Hiemke C, Grunder G, et al: Reduced clearance of venlafaxine in a combined treatment with quetiapine. *Progress in Neuropsychopharmacology & Biological Psychiatry* 2018;85 (July):116–121. From Aachen University, Germany; and other institutions. **This research was conducted without funding. Three authors disclosed relevant relationships with commercial sources; the remaining 3 authors declared no competing interests.**

Common Drug Trade Names*: quetiapine—*Seroquel*; venlafaxine—*Effexor

Lamotrigine Immune System Reaction

The FDA has issued a warning that the anticonvulsant lamotrigine (*Lamictal*) can cause hemophagocytic lymphohistiocytosis (HLH), a rare but serious immune system reaction that can result in severe inflammation throughout the body. HLH triggers an uncontrolled immune response that can lead to serious liver, kidney, lung, and blood cell issues. Patients with HLH typically present with persistent fever, rash, or other nonspecific symptoms. The diagnosis of HLH is based upon the patient exhibiting ≥5 of the following 8 symptoms: fever and rash; enlarged spleen; cytopenia; elevated triglyceride levels or low fibrinogen levels; high serum ferritin levels; hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy; decreased or absent natural killer cell activity; or elevated blood levels of CD25 indicating prolonged immune cell activation. Lamotrigine should be discontinued if HLH is suspected.

Lamictal (lamotrigine): Drug Safety Communication - Serious Immune System Reaction. Available at https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm605628.htm.

Safety of Clozapine Rechallenge

According to a review of published case reports, rechallenge with clozapine (*Clozaril*) may be an option for patients who have stabilized following drug-induced neutropenia or neuroleptic malignant syndrome. Rechallenge after agranulocytosis or myocarditis is not advised.

Methods: A literature search was undertaken to identify all reports of rechallenge after adverse reactions to clozapine reported in 1971–2017. The rechallenge was considered successful if the patient did not experience the previous complication or any other serious adverse event during the reported follow-up interval. The outcome of rechallenge after each complication was considered favorable if there were ≥5 reported cases and more than half were successful.

Results: The search identified 259 clozapine rechallenge reports, all of which were single case reports. Rechallenge was successful in 157 patients (61%). Outcome was favorable in 3 of 17 cases of agranulocytosis (18%), 128 of 203 cases of neutropenia (63%), 11 of 17 cases of myocarditis (65%), and all 7 cases of neuroleptic malignant syndrome (100%). There were also isolated reports of successful rechallenge following eosinophilia, cardiac complications other than myocarditis, and gastrointestinal hypermotility. Rechallenge was unsuccessful in 3 cases of pancreatitis, 2 of renal insufficiency, and 1 of clozapine-induced lupus. No fatal outcomes were reported in any of the cases.

Discussion: Based on the reviewed case reports, the authors conclude that clozapine-associated agranulocytosis, pancreatitis, renal failure, and lupus should be considered "nonrechallengeable." Seemingly positive results after myocarditis should be interpreted cautiously because of the small number of cases reported.

Manu P, Lapitskaya Y, Shaikh A, Nielsen J: Clozapine rechallenge after major adverse effects: clinical guidelines based on 259 cases. *American Journal of Therapeutics* 2018; doi 10.1097/MJT.0000000000000715. From Hofstra Northwell School of Medicine, Hempstead, NY; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Clozapine and All-Cause Mortality

Continuous use of clozapine (*Clozaril*) was associated with reduced mortality compared with other antipsychotics in a meta-analysis of studies lasting >1 year. This observation calls into question existing concern that clozapine-associated cardiovascular effects may increase mortality risk.

Methods: A comprehensive literature search identified studies published through March 2018 conducted in patients with schizophrenia spectrum disorders who received treatment with clozapine and were followed for >1 year. Included studies were required to have mortality as an outcome, and rates were compared between patients treated continuously or ever with clozapine or other antipsychotics.

Results: The analysis included 24 studies (1 randomized trial and 23 observational studies) with a median follow-up of 5.4 years and a maximum of 12.5 years. Crude mortality rates in patients who used clozapine varied widely across the studies, from 0 to 41 per 1000 patient-years. Mortality did not differ substantially in studies that reported continuous versus ever use of clozapine, or as a function of demographic or study characteristics. A comparison of patients who took clozapine throughout a mean observation period of >7 years found that compared with continuous use of other antipsychotics, clozapine was associated with a significant reduction in mortality (crude mortality rate ratio, 0.56; p=0.007). Mortality rates were numerically but not significantly lower in studies of patients ever exposed to clozapine compared with those exposed to other antipsychotics (mortality rate ratio, 0.74). In the few studies that compared any use of clozapine with no antipsychotic use, clozapine had a mortality rate ratio of 0.34 (p≤0.001).

Data were inconsistent or insufficient to analyze clozapine effects on specific causes of death. However, 13 studies reported data on suicide mortality. Rates ranged widely in individual studies, and patients exposed to clozapine compared with other antipsychotics were found to have a numerically lower suicide rate that did not reach statistical significance.

Discussion: These findings suggest that benefits of continuous clozapine use in prolonging life expectancy may be diminished or lost when the drug is discontinued. Possible explanations for the reduced mortality with clozapine include superior efficacy, leading to improved function and self-care, and closer clinical monitoring and surveillance.

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

Vermeulen J, van Rooijen G, van de Kerkhof M, Sutterland A, et al: Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1–12.5 years. *Schizophrenia Bulletin* 2018; doi 10.1093/schbul/sby052. From the University of Amsterdam, the Netherlands; and other institutions. **Source of funding not stated. One of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Aripiprazole–Sertraline in Resistant Depression

In a manufacturer-sponsored trial, a combined formulation of aripiprazole and sertraline was superior to sertraline plus placebo in patients with resistant depression.[1] Aripiprazole is FDA approved as adjunctive treatment for antidepressant-resistant depression, and research in other medical specialties has shown that adherence may be improved with fixed-dose combination preparations as opposed to separate pills.[2]

Methods: The trial recruited patients in Asia and Australia who met DSM-5 criteria for major depressive disorder, with the current episode lasting ≥8 weeks and nonresponsive to 1–3 courses

of adequate antidepressant medication. After their baseline medication was tapered to a level considered safe for switching, patients were required to meet a minimum symptom score of ≥18 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Qualifying patients received sertraline monotherapy for 8 weeks. Inadequate response was defined as a <50% reduction in HAM-D score, a HAM-D score of ≥14, and a Clinical Global Impression (CGI) Improvement* score of ≥3. Patients who experienced an inadequate response to sertraline at week 8 were randomly assigned to receive aripiprazole–sertraline, formulated as a single tablet, or a placebo–sertraline combination. The active study medication contained 3, 6, 9, or 12 mg aripiprazole and 100 mg sertraline. Aripiprazole was titrated to the minimum effective/maximum tolerated dose by week 4, and treatment was continued through 6 weeks. The primary efficacy measure was mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: Of 735 patients who completed the sertraline monotherapy phase, 412 (average age, nearly 40 years; 63% men) had an inadequate response and entered the randomized study phase. More than 90% of these patients completed the full trial. At study endpoint, 27% of patients were receiving aripiprazole at 3 mg/day, 23% at 6 mg/day, 12% at 9 mg/day, and 38% at 12 mg/day.

The mean MADRS score, about 25 at baseline, decreased by 9.2 points in the aripiprazole–sertraline group and by 7.2 points in the placebo–sertraline group (p=0.007). Differences were statistically significant beginning by week 1 of double-blind treatment. The MADRS response rate (≥50% decrease) was 37.5% with the active combination and 25.6% with the placebo combination (p<0.05; odds ratio,* 1.73). Remission rates (MADRS ≤10) were 29.3% and 20.2%, respectively (p<0.05; odds ratio, 1.65). Secondary outcome measures, including CGI Improvement and Severity scores, the HAM-D, and measures of apathy and social adaptation, all showed significantly greater improvement with aripiprazole–sertraline.

Akathisia occurred in 12.9% of the aripiprazole–sertraline group and 3.4% of the placebo–sertraline group. Other adverse effects occurred in similar proportions of the 2 treatment groups. Weight gain of ≥7% occurred in nearly 10% of patients who received aripiprazole and <2% of the comparison group (p=0.0003).

Discussion: These observations are similar to those observed in previous trials of aripiprazole augmentation using separate pills. The low incidence of akathisia, relative to other trials, may be due to the relatively low aripiprazole dose.

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

[1]Kamijima K, Kimura M, Kuwahara K, Kitayama Y, et al: A randomized, double-blind comparison of aripiprazole/sertraline combination and placebo/sertraline combination in patients with major depressive disorder. *Psychiatry and Clinical Neurosciences* 2018; doi 10.1111/pcn.12663. From Showa University; and other institutions including Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan. **Funded by Otsuka. All 5 study authors declared financial relationships with commercial sources, including Otsuka.**

[2]van Galen K, Nellen J, Nieuwkerk P. The effect on treatment adherence of administering drugs as fixed-dose combinations versus as separate pills: systematic review and meta-analysis. *AIDS Research and Treatment* 2014; 2014: 967073.

Common Drug Trade Names*:** **aripiprazole—*Abilify*; sertraline—*Zoloft

***See Reference Guide.**

Mazindol for Adult ADHD

In a phase-II placebo-controlled trial, controlled-release mazindol was effective in adults with ADHD, with an effect size comparable to stimulants. Mazindol is a serotonin, noradrenaline, and dopamine reuptake inhibitor (SNDRI) previously introduced for treatment of obesity but withdrawn from the market because of low sales. This is the first clinical trial

of a controlled-release formulation, following promising results of an open-label study of immediate-release mazindol in children with ADHD.

Methods: Study participants were adults, aged 18–65 years, with a diagnosis of ADHD meeting minimum severity criteria when unmedicated. Those with concurrent DSM-5 disorders requiring treatment were excluded. Patients received mazindol or placebo for 6 weeks, with mazindol dosed flexibly within a range of 1–3 mg/day. The primary efficacy measure was change from baseline in the ADHD Rating Scale for DSM-5 (ADHD-RS-DSM5). Efficacy was also assessed with the Clinical Global Impression–Improvement* (CGI-I) scale and with the Target Impairment Scale, which measures changes in 3 functional goals selected by the patient.

Results: A total of 84 patients (42% men) were randomized and had ≥1 post-baseline assessment. Average patient age was 33–35 years; 42% were moderately ill, 51% were markedly ill, and 7% were severely ill according to the CGI–Severity scale. Nearly 30% were ADHD medication-naive. A total of 5 patients did not complete the study—2 in the mazindol group and 3 in the placebo group—all because of noncompliance or protocol violations. By week 4, after which dosage changes were not allowed, 10 patients were receiving 2 mg/day mazindol and 31 were receiving 3 mg/day.

The mean ADHD-RS-DSM5 score at baseline was 39. Mazindol was associated with a significantly larger improvement after 6 weeks of treatment (19 vs 6 points; $p<0.001$; effect size,* 1.09). Effects of mazindol differed statistically from placebo after the first week of treatment, and differences grew larger over the subsequent weeks. Significantly more patients were classified as "excellent responders" (≥50% improvement on the ADHD-RS-DSM5) in the mazindol group beginning at 2 weeks. By 6 weeks, 55% of the mazindol group and 16% of the placebo group were classified as excellent responders ($p=0.002$). CGI-I ratings of much or very much improved were observed in 62.5% of the mazindol group and 21% of the placebo group ($p<0.001$). Improvement in target areas was also significantly greater with mazindol.

The most common adverse effects of mazindol, relative to placebo, were dry mouth, nausea, fatigue, increased heart rate, decreased appetite, and constipation. Patients receiving mazindol lost an average of nearly 4 lbs during the 6-week study. However, previous experience indicates the effects of mazindol on weight are short-lived.

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

Wigal T, Newcorn J, Handal N, Wigal S, et al: A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs* 2018;32 (March):289–301. From AVIDA Inc., Newport Beach, CA; and other institutions. **Funded by NLS-1 Pharma AG. All study authors disclosed relevant financial relationships with NLS-1 Pharma AG and other sources.**

Common Drug Trade Names*: mazindol (not available in the U.S.)—*Mazanor, Sanorex

***See Reference Guide.**

Lofexidine for Opioid Withdrawal Symptoms

Physical dependence is an expected physiological response to opioid use. In patients using the medications appropriately, opioid withdrawal is typically accomplished using a slow taper. In patients with opioid use disorder, the abused medication is typically replaced with an alternate opioid medicine, which is then gradually reduced and followed by transition to maintenance therapy with an agent such as methadone, buprenorphine, or naltrexone.

The FDA recently approved lofexidine hydrochloride, the first nonopioid medication for the alleviation of opioid withdrawal symptoms in adults in order to expedite abrupt discontinuation. Lofexidine is a selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine, the effects of which are thought to have a role in many of the symptoms of

opioid withdrawal. The newly approved drug is not a treatment for opioid use disorder; however, it can lessen the severity of withdrawal symptoms including anxiety, agitation, sleep difficulty, muscle ache, runny nose, sweating, nausea, vomiting, diarrhea, and drug craving. In clinical trials, the most common adverse effects associated with lofexidine were hypotension, bradycardia, somnolence, sedation, and dizziness. Because lofexidine can affect cardiac conduction, patients may experience a marked blood pressure increase when the agent is stopped. Safety and efficacy have not been established in children or adolescents, and the approval covers only a 14-day course of treatment in adult patients.

FDA News Release: FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm.

Common Drug Trade Names*: buprenorphine—*Buprenex*; lofexidine—*Lucemyra*; methadone—*Methadose*; naltrexone—*ReVia

Cardiovascular Safety of Antismoking Agents

In a large trial in a general population of smokers with or without established psychiatric disorders, smoking cessation medications were not associated with cardiovascular risk.

Background: Early clinical trials of bupropion and varenicline did not show excess risk of cardiovascular events in treated patients. However, in 2011, the FDA mandated that smoking-cessation medications carry warnings of possible cardiovascular events in smokers with established cardiovascular disease. Findings of subsequent studies were mixed, and the FDA mandated the extension of a large clinical trial to monitor cardiovascular safety.

Methods: Participants in the original multinational study were adults, aged 18–75 years, who smoked ≥10 cigarettes per day and wanted to quit. Those with recent clinically significant cardiovascular or cerebrovascular disease were excluded. Randomized treatment, provided for 24 weeks in a triple-dummy fashion, consisted of 1 mg varenicline b.i.d., 150 mg bupropion b.i.d., a nicotine-replacement patch as an active control, or placebo. Patients were invited to participate in the extension study regardless of whether they stopped study medication prematurely, as long as they remained in follow-up throughout the 24-week trial. During the nontreatment extension, patients were evaluated in the clinic every 4 weeks up to week 52. The primary outcome was time to a major adverse cardiovascular event (i.e., cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke). The incidence of these events was compared during treatment, during the 30 days after completion, and at 1 year.

Results: More than 8000 patients received randomized medication or placebo in the original 24-week study. Their average age was 46 years, 44% were men, and about half had a neuropsychiatric disorder. Between 77% and 79% of each treatment group completed the 24-week trial, and 56% of the original cohort enrolled in the extension trial. Of this group, 90% completed the additional half year of follow-up. Patients were exposed to medication (or placebo) an average of about 74 days.

Major adverse cardiovascular events were infrequent, occurring in <0.5% of all groups. Overall there were 14 nonfatal MIs, 8 nonfatal strokes, and 5 cardiovascular deaths. The groups also did not differ in time to major adverse cardiovascular event or a composite outcome consisting of a major adverse cardiovascular event plus new-onset or worsening peripheral vascular disease requiring treatment, coronary revascularization, or hospitalization for unstable angina. Results of the analysis did not differ for each of the 3 observation periods or in patients in low, medium, or high baseline cardiovascular risk categories.

Discussion: Participants in the present study were in generally good health and representative of the population of smokers in general medical practice. No evidence was found in these patients that smoking-cessation agents increase the risk of serious cardiovascular events during

or after treatment. In addition, the number of adverse cardiac events that did occur was small and the incidence of serious events was low, suggesting that any absolute increase in risk is low and not clinically meaningful.

Benowitz N, et al: Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.0397. From the University of California, San Francisco; and other institutions. **Funded by Pfizer; and GlaxoSmithKline. All 9 study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

Common Drug Trade Names*: bupropion—*Zyban*; nicotine patch—*Nicoderm*; varenicline—*Chantix

Brexpiprazole Versus Lurasidone

In a network meta-analysis that compared placebo-controlled acute treatment trials in patients with schizophrenia, brexpiprazole and lurasidone were found to have similar efficacy. However, lurasidone was associated with somewhat less weight gain and better metabolic outcomes.

Background: Metabolic effects and weight gain can be problematic with atypical antipsychotic treatment, and weight-neutral options may be an important consideration for patients with potential metabolic issues. Brexpiprazole and lurasidone are both believed to have neutral effects on weight, but there have been no head-to-head comparisons reported.

Methods: The analysis, conducted by the manufacturer of lurasidone, identified phase II, III, or IV trials of the drugs that were published or presented at major conferences through the third quarter of 2015. Trials were included if they had ≥1 arm treated with the FDA-approved doses of either drug and assessed the efficacy of the drug at reducing symptoms of schizophrenia during acute episodes. Using placebo as a common comparator, outcomes were compared over 6 weeks of treatment. The primary efficacy outcome was response, defined as a ≥20% decrease in the Positive and Negative Syndrome Scale (PANSS) score. Metabolic outcomes were the proportion of patients gaining ≥7% of their baseline weight as well as mean changes in weight, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Results: The analysis included 3 trials of brexpiprazole and 5 trials of lurasidone. Patient populations were generally comparable with regard to age, gender, disease severity, and baseline metabolic characteristics or weight. Response rates did not differ significantly between the 2 drugs, ranging from 39% to 53% for brexpiprazole and from 44.4% to 63.2% for lurasidone. Differences in the response rates and mean changes in the PANSS and the Clinical Global Impression–Severity scale scores favored lurasidone but were not statistically significant.

At 6 weeks, patients receiving lurasidone were less likely to gain ≥7% of their baseline weight, although the between-group difference was not statistically significant (odds ratio,* 0.50). Patients taking lurasidone gained significantly less weight than those receiving brexpiprazole (mean difference, 1.5 lbs) and had significant reductions in total and LDL cholesterol relative to brexpiprazole (about 7 mg/dL each).

Discussion: Long-term studies and head-to-head comparisons are required to determine if the differential effects of these drugs on weight and lipid metabolism are lasting and whether the reduced weight gain with lurasidone translates to improved cardiovascular outcomes.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, individual study quality does not appear to have been systematically evaluated.

Ng-Mak D, Tongbram V, Ndirangu K, Rajagopalan K, et al: Efficacy and metabolic effects of lurasidone versus brexpiprazole in schizophrenia: a network meta-analysis. *Journal of Comparative Effectiveness Research* 2018; doi 10.2217/cer-2018–0016. From Sunovion Pharmaceuticals, Inc., Marlborough, MA; and ICON Health Economics, New York, NY. **Funded by Sunovion. All study authors disclosed relevant financial relationships with commercial sources including Sunovion or ICON Health Economics.**

Common Drug Trade Names*: brexpiprazole—*Rexulti*; lurasidone—*Latuda

***See Reference Guide.**

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

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.

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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