

PSYCHIATRY DRUG ALERTS

Antidepressant/Warfarin Interaction	81
Beta-Blockers for Violence Prevention.....	87
Bupropion vs Paroxetine for Suicidality	83
Clozapine and Eosinophilia	86
Generic Olanzapine.....	81
IM Haloperidol: Needle Length.....	82
Quetiapine QT Prolongation	86
Reference Guide	88
Therapeutic Drug Monitoring.....	84
Varenicline Safety Update	82
Zonisamide Augmentation.....	85

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Generic Olanzapine Approved

The FDA has approved the first generic versions of *Zyprexa* (olanzapine) and *Zyprexa Zydys* (olanzapine orally disintegrating tablets) for the treatment of schizophrenia and bipolar disorder. The generic versions have the same quality, strength, and purity as the brand-name agents, and the manufacturing, packaging, and testing sites must meet the same quality standards. Generic olanzapine tablets will be manufactured by Dr. Reddy's Laboratories and Teva Pharmaceuticals, and the *Zydys* formulation will be manufactured by Apotex, Dr. Reddy's Laboratories, and Par Pharmaceuticals.

FDA News Release: FDA approves first generic olanzapine to treat schizophrenia, bipolar disorder. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Antidepressant/Warfarin and GI Bleeding

According to results of a case-control study, patients receiving chronic warfarin therapy have an increased risk of GI bleeding after receiving a new prescription for an antidepressant. The excess risk appears to decline with subsequent prescriptions.

Methods: Medicaid enrollees from 5 large U.S. states, which account for about one-third of the country's Medicaid population, comprised the study sample. Case patients were those prescribed warfarin between 1999 and 2005 who were hospitalized for GI bleeding during this period. Each case was matched with 50 controls (warfarin users who did not experience GI bleeding). The analysis included only antidepressants initially prescribed after a period of warfarin use. All antidepressants, regardless of drug class, were considered if they were listed as potentially interacting agents with warfarin in commonly used U.S. drug-interaction compendia.

Results: The incidence of hospitalization for GI bleeding in the entire patient population was about 4.5 per 100 person-years of warfarin use. Of the 9 antidepressants, all but nortriptyline

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were associated with a statistically significant risk of GI bleeding, with odds ratios* ranging from 1.51 to 2.49. In an analysis adjusted for multiple factors (e.g., age; gender; nursing home placement; concomitant illness; use of acetaminophen, levofloxacin, or proton pump inhibitors), the associations with escitalopram, sertraline, and venlafaxine were no longer statistically significant, although all still had elevated odds ratios. The association with GI bleeding remained statistically significant for citalopram, fluoxetine, paroxetine, amitriptyline, and mirtazapine. Citalopram and mirtazapine had the highest odds ratios in the adjusted analysis, at about 1.7. The excess risk of GI bleeding was associated only with the first prescription for an antidepressant and did not extend to second, third, and fourth prescriptions.

Discussion: Depression often coexists with cardiovascular disease. About 7% of patients using warfarin are also given a prescription for antidepressants, which can interact with warfarin by interfering with its metabolism and by blocking serotonin reuptake by platelets. Previous studies of bleeding risk have had conflicting results, possibly because investigators assumed that bleeding risk would be constant after introduction of the antidepressant. The present study assumed that risk would be limited to the early period because susceptible patients would develop GI bleeding soon after antidepressants were prescribed and then discontinue treatment or change the antidepressant.

Schelleman H, Brensinger C, Bilker W, Hennessy S: Antidepressant-warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. *PLoS One* 2011;6(6):e21447. From the University of Pennsylvania, Philadelphia. Funded by the National Institute on Aging. The study authors disclosed financial relationships with commercial sources.

Drug Trade Names: amitriptyline—*Elavil, Endep, Enovil*; citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; levofloxacin—*Levaquin*; mirtazapine—*Remeron*; nortriptyline—*Aventyl, Pamelor*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Varenicline Neuropsychiatric Safety Update

In 2007 the FDA issued a warning about suicidal thoughts and aggressive behavior in patients using varenicline (*Chantix*) for smoking cessation. In 2008 another report suggested the neuropsychiatric symptoms were likely associated with the drug rather than with nicotine withdrawal. Since that time, 2 FDA-sponsored epidemiological studies have examined the neuropsychiatric adverse effects of varenicline in patients trying to quit smoking. Neither study found a significant difference in serious neuropsychiatric events (i.e., that required hospitalization) between varenicline and nicotine-replacement therapies such as *NicoDerm* patches. These studies had serious limitations, including small samples and only evaluating events that precipitated hospitalization. The manufacturer is currently conducting a large-scale study to evaluate the neuropsychiatric safety of varenicline. The results are expected in 2017. Until then, prescribers are urged to monitor patients who are taking the drug for agitation, depressed mood, behavioral changes, and suicidal thoughts.

FDA drug safety communication: safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. Available at www.fda.gov/Drugs/DrugSafety/ucm276737.htm.

IM Haloperidol: Needle Length Matters

Intramuscular antipsychotic administration increases compliance and can improve relapse prevention efforts as well as reduce hospitalization. If the expected results are not being observed with IM administration, the effects of patient-specific characteristics, such as adiposity in the administration area, should be evaluated. In patients with prominent distribution of adipose tissue, increasing needle length may improve medication effects.

A 23-year-old female with schizophrenia had been treated with consecutive trials of IM haloperidol and fluphenazine with minimal success and was subsequently lost to follow-up. When she presented with continual auditory hallucinations and paranoid delusions, treatment was restarted with 5 mg b.i.d. oral haloperidol and monthly 150-mg IM gluteal injections of haloperidol decanoate using a 1.5-inch needle. Because of continued psychosis, the haloperidol decanoate dosage was increased to 350 mg administered every 3 weeks. The patient continued to experience auditory hallucinations. Excess gluteal fat distribution was considered as a possible factor in this patient's nonresponse. Following a switch to a 2-inch needle, the patient noticeably improved and her improvement progressed.

The prescribing information for haloperidol decanoate includes instructions for needle gauge, but not length. Other IM antipsychotic labels include instructions regarding needle gauge and length based on administration site and patient weight. Generally, longer needle lengths are recommended for gluteal injections in patients with obesity.

Brahm N, Washington N: Case report: increased patient response to intramuscular haloperidol decanoate following a change in needle length. *Journal of Pharmacy Practice* 2011;doi 10.1177/0897190011426559. From the University of Oklahoma, Tulsa. **The authors disclosed no competing interests.**

Drug Trade Names: fluphenazine—*Prolixin*; haloperidol—*Haldol*

Bupropion vs Paroxetine for Suicidal Behavior

Results of a pilot study suggest paroxetine may be modestly superior to bupropion at reducing suicidal ideation in a subgroup of high-risk adults with depression. Patients with the most severe suicidal ideation at baseline appeared to experience the greatest improvement with paroxetine.

Methods: Study subjects were 74 patients with a current major depressive episode and a past suicide attempt, current suicidal ideation, or both. Patients received flexible-dose extended-release paroxetine (starting at 25 mg/day, increasing to 37.5–50 mg/day) or bupropion (starting at 150 mg/day, increasing to 300–450 mg/day). Treatment outcomes were evaluated weekly for 8 weeks of acute treatment, followed by monthly evaluations for an additional 16 weeks. Suicidal behavior during follow-up was assessed with the Clinical Scale for Suicidal Ideation.

Results: A total of 24 patients (32%) did not complete acute treatment, and only 21 finished the full 24-week protocol. During the study period, there were 10 suicidal events: 4 in the paroxetine group and 6 in the bupropion group (3 of these events occurred in a single patient). Most of the events (n=9) comprised increased ideation or agitation. A single patient was hospitalized for an acetaminophen overdose.

Overall, improvements in suicidal ideation and depression did not differ substantially between the groups. However, paroxetine produced greater improvements than bupropion in depression among patients with more severe depressive symptoms (other than suicidality) at baseline. Similarly, improvements in suicidal ideation were greater with paroxetine than with bupropion in these patients. Among those with the most severe suicidal ideation at baseline, bupropion was associated with a nearly 6-times greater risk than paroxetine of worsening ideation.

Discussion: It appears that there have been no antidepressant clinical trials previously conducted in patients chosen for elevated suicide risk. Suicidal behavior is known to be associated with serotonergic hypofunction, but studies comparing serotonergic with noradrenergic antidepressants have not consistently favored either drug class. Although the

high attrition rate and large variability in treatment outcomes limit the ability of this study to assess a selective effect of an SSRI on suicidal behavior, results suggest a larger clinical trial is warranted.

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

Grunebaum M, Ellis S, Duan N, Burke A, et al: Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology* 2011; doi 10.1038/npp.2011.247. From Columbia University and New York State Psychiatric Institute, New York, N.Y. **Funded by the National Alliance for Research on Schizophrenia and Depression; and the NIMH.**

Drug Trade Names: bupropion—*Wellbutrin*; paroxetine—*Paxil*

*See Reference Guide.

Therapeutic Drug Monitoring in Psychiatry

With the vast number of psychoactive drugs available today, therapeutic drug monitoring (TDM; the quantification of serum or plasma concentrations of medications for dose optimization) can be a valuable tool for optimizing drug dosages. In 2004 guidelines were released for the use of TDM in psychiatric patients. Since that time, knowledge of TDM and pharmacogenetics has advanced substantially, and an update to the guideline was recently released.

Of 128 neuropsychiatric drugs evaluated, TDM was "strongly recommended" for 15, "recommended" for 52, considered "useful" for 44, and "potentially useful" for 19. See table for TDM reference ranges for several commonly evaluated drugs.

TDM is strongly recommended for most TCAs, but is of little use for most SSRIs, except in elderly patients for whom it may help determine a minimum effective dosage. Early plasma concentrations of citalopram may be useful in predicting later nonresponse. Evidence does not support TDM for tetracyclic antidepressants or MAOIs. TDM is strongly recommended for the first-generation antipsychotics haloperidol, perphenazine, and fluphenazine, and the second-generation agents amisulpride, clozapine, olanzapine, and risperidone. Therapeutic ranges are well defined for lithium, valproic acid, and carbamazepine, and TDM is strongly recommended for these

Reference Ranges for Psychoactive Drugs for Which TDM is Strongly Recommended	
Drug Name	Therapeutic Reference Range
Antidepressants	
Amitriptyline	80–200 ng/mL
Clomipramine	230–450 ng/mL
Desipramine	100–300 ng/mL
Imipramine	175–300 ng/mL
Nortriptyline	70–170 ng/mL
Antipsychotics	
Amisulpride	100–320 ng/mL
Haloperidol	1–10 ng/mL
Fluphenazine	1–10 ng/mL
Perphenazine	0.6–2.4 ng/mL
Clozapine	350–600 ng/mL
Olanzapine	20–80 ng/mL
Risperidone	20–60 ng/mL
Mood Stabilizers	
Lithium	0.5–1.2 mmol/l
Carbamazepine	4–10 mcg/mL
Valproic Acid	50–100 mcg/mL

drugs. For antidementia drugs (e.g., donepezil, rivastigmine) and anxiolytic/hypnotic drugs (e.g., benzodiazepines), TDM is rarely used but may be useful. Calculated therapeutic reference ranges are scarce for dopamine agonists and other antiparkinsonian drugs, and the efficacy of TDM has not been established.

TDM recommendations are also based on patient-specific factors. It is strongly recommended for pregnant or breastfeeding patients, children and adolescents, patients with intellectual disabilities, and the elderly. Plasma measurements can also be useful for: dose optimization; suspected complete or partial-medication noncompliance; when there is a lack of improvement with recommended doses; if adverse effects occur; with a suspected drug interaction; for relapse prevention with maintenance treatment; in the presence of a particularity concerning genetic polymorphism; and for patients with pharmacokinetically relevant comorbidities (e.g., hepatic or renal insufficiency, cardiovascular disease). Because concentrations outside of the reference range may be caused by genetic polymorphisms, pharmacogenetic studies may also be undertaken to determine if a patient is a "poor" or "ultrarapid" metabolizer, which can guide dosing decisions.

Hiemke C, Baumann P, Conca A, Dietmaier O, et al: AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 2001; 44:195–235. From University Medical Center, Mainz, Germany; and other institutions. **Source of funding not stated. Several study authors disclosed financial relationships with commercial sources.**

Drug Trade Names: amisulpride (not available in the U.S.)—*Deniban, Solian*; amitriptyline—*Elavil, and others*; carbamazepine—*Epitol, Tegretol*; citalopram—*Celexa*; clomipramine—*Anafranil*; clozapine—*Clozaril*; desipramine—*Norpramin*; donepezil—*Aricept*; fluphenazine—*Prolixin*; haloperidol—*Haldol*; imipramine—*Tofranil*; nortriptyline—*Aventyl, Pamelor*; olanzapine—*Zyprexa*; perphenazine—*Trilafon*; risperidone—*Risperdal*; rivastigmine—*Exelon*; valproic acid—*Depakene, Depakote*

Antidepressant Augmentation with Zonisamide

In a pilot study, zonisamide showed promise as augmentation therapy in patients with unipolar major depression receiving duloxetine.

Background: Zonisamide is FDA approved as an anticonvulsant and is commonly used to augment antiparkinsonian drugs. It has the ability to enhance dopaminergic and serotonergic neurotransmission. In the present open-label, uncontrolled study, its use was investigated as an adjunct to duloxetine, chosen because the 2 agents have little potential for pharmacokinetic interaction.

Methods: Study participants were 40 adults experiencing a major depressive episode. All patients were initially treated with 60 mg/day duloxetine for 12 weeks. Those who did not achieve clinical response (i.e., $\geq 50\%$ reduction in the 17-item Hamilton Rating Scale for Depression [HAM-D] total score) went on to receive 75 mg/day zonisamide, in addition to their duloxetine, for another 12 weeks.

Results: After the initial 12 weeks, 15 patients had responded to duloxetine and 1 dropped out of the study. Of the remaining 24 patients who received zonisamide augmentation, 14 achieved response by week 24. Thus by study end, 29 of 40 patients (73%) had responded to either duloxetine or the combination.

Adverse effects were reported at 12 weeks and then at 24 weeks in the patients who went on to receive the zonisamide. During duloxetine monotherapy, some adverse effects—*anorgasmia, poor concentration, and general malaise*—were reported more commonly in nonresponders than responders. During the 12-week augmentation period, *insomnia* was the only adverse effect reported by patients who had an antidepressant response. Among the 10 nonresponders to augmentation, *poor concentration and reduced energy* were

reported by all, loss of libido by 8, and anorgasmia by 6. No patient had a manic episode. Unexpectedly, patients who received zonisamide experienced significant weight loss between weeks 12 and 24, averaging >6 lbs in those with an antidepressant response and 3 lbs in nonresponders.

Discussion: Although the study had important methodological limitations, including the small sample size, low duloxetine dose, and particularly the lack of a placebo control, the results indicate that zonisamide may be an acceptable augmentation strategy in patients with major depression. Further studies with rigorous designs are warranted before definitive conclusions can be drawn.

Fornaro M, Martino M, Dalmasso B, Colicchio S, et al: An open pilot study of zonisamide augmentation in major depressive patients not responding to a low dose trial with duloxetine: preliminary results on tolerability and clinical effects. *Annals of General Psychiatry* 2011;10:23. From the University of Genova, Genoa, Italy; and other institutions. Source of funding not stated. The authors disclosed no competing interests.

Drug Trade Names: duloxetine—*Cymbalta*; zonisamide—*Zonegra*

Quetiapine and QT Prolongation

The FDA recently required the addition of a warning about QT-interval prolongation, which can lead to torsades de pointes, to the labeling for quetiapine (*Seroquel*). The warning stemmed from reports of QT prolongation in patients with concomitant illness, those who were taking other medications that affect the QT interval or cause electrolyte imbalance, and in cases of overdose. Several drugs are listed in the quetiapine labeling as concomitant medications to avoid: the antiarrhythmics procainamide, quinidine, amiodarone, and sotalol, and the antibiotic moxifloxacin as well as chlorpromazine, thioridazine, and ziprasidone. QT prolongations are more likely to occur with increasing doses and in patients with elevated serum concentrations because of renal or hepatic insufficiency. Resulting torsades de pointes occurs more frequently in women and the elderly than in other populations. Other second-generation antipsychotics also have the potential to prolong the QT interval. Risk appears to be lowest with aripiprazole and lurasidone, which may be better options for patients taking other QT affecting drugs or at increased risk of complications from the prolongation.

Quetiapine (*Seroquel*) and QT-interval prolongation. *The Medical Letter* 2011;53 (October 3):79.

Drug Trade Names: amiodarone—*Cordarone, Pacerone*; aripiprazole—*Abilify*; chlorpromazine—*Thorazine*; lurasidone—*Latuda*; moxifloxacin—*Avelox*; procainamide—*Procanbid, Pronestyl*; quetiapine—*Seroquel*; quinidine—*Quinidex, and others*; sotalol—*Betapace, Sorine*; thioridazine—*Mellaril*; ziprasidone—*Geodon*

Clozapine-Associated Benign Eosinophilia

A 27-year-old male had an 8-year history of paranoid schizophrenia for which he had been hospitalized several times. Multiple antipsychotic trials produced little or no improvement. Treatment with clozapine produced notable improvement in both positive and negative symptoms within days, but tachycardia, fever, and eosinophilia developed over the first few weeks of treatment. Clozapine was replaced with relatively high-dose haloperidol, olanzapine, and aripiprazole. Psychotic symptoms improved, but the patient remained markedly impaired, both functionally and socially. When the patient's condition deteriorated, clozapine rechallenge was considered, and a slow dose titration was started. Other psychotropics were tapered and discontinued, and the patient was monitored with near daily blood draws. Clozapine was titrated in ≤ 25 -mg increments every few days. Psychotic symptoms improved, but the patient's eosinophil count gradually increased to 13% of the total white blood cell (WBC) count. There were no cardiac symptoms or fever, other laboratory values were within acceptable ranges, and the patient did not exhibit signs of organ involvement. Eosinophilia reached a peak of 16% of

the total WBC count at a clozapine dosage of 150 mg/day. Over the subsequent 5 weeks, the eosinophil counts decreased and then remained within the normal range with clozapine dosages ≤ 300 mg/day over 1 year of continued treatment.

Blood dyscrasias are a well known potential adverse effect of clozapine. Eosinophilia has been reported and is believed to be a marker for potentially serious inflammatory conditions in clozapine-treated patients. No specific monitoring recommendations for eosinophilia exist, and proper management of clozapine-associated eosinophilia has been debated. Patients in whom agranulocytosis or other blood dyscrasias develop often rapidly re-experience the reaction on rechallenge. According to the present case report, as well as previously described patients, it appears that clozapine may be safely continued in patients with eosinophilia without signs or symptoms of organ damage.

Roberts C, Mortenson L, Merrill D, Rafizadeh N, et al: Successful rechallenge with clozapine after eosinophilia. *American Journal of Psychiatry* 2011;168 (November):1147–1151. From Columbia University, New York, N.Y. **One study author disclosed financial relationships with several pharmaceutical sources.**

Drug Trade Names: aripiprazole—*Abilify*; clozapine—*Clozaril*; haloperidol—*Haldol*; olanzapine—*Zyprexa*

Violence Prevention with Beta-Blockers

Beta-blockers have long been used in the management of acute aggression in a variety of settings. Limited evidence supports prophylactic use to prevent aggressive behavior. Two cases are presented here.

A 40-year-old male with bipolar schizoaffective disorder was hospitalized with delusions and violent behavior. His delusions became less prominent with monthly injections of 100-mg fluphenazine decanoate plus oral clonazepam, quetiapine, and trihexyphenidyl, but he remained aggressive and impulsive. With a trial of pindolol, initiated at 5 mg b.i.d. and quickly increased to 10 mg b.i.d., the patient reported feeling significantly calmer. Within days he was no longer experiencing aggressive or violent outbursts. Continued pindolol, administered only if the patient's pulse was ≥ 60 , was well tolerated, and he was discharged with no violent behavior to a group home.

A 20-year-old male outpatient with antisocial personality disorder had been unsuccessfully treated for a number of years with a wide variety of psychotropics, including antipsychotics, antidepressants, mood stabilizers, stimulants, and anxiolytics. The patient described himself as having difficulty controlling his emotions and "felt angry all the time." He consented to a trial of 40 mg propranolol b.i.d. Despite only taking half of the prescribed doses, the patient and his case worker reported improvement in his temper over the next several weeks and he was noticeably calmer and less agitated. He reported no adverse effects of propranolol treatment, and positive effects were maintained at 6-month follow-up.

These case reports add to the evidence supporting prophylactic beta-blockers for violence prevention. However, appropriate patients must be carefully selected because of potentially serious adverse effects. Beta-blockers are contraindicated in patients with asthma, bradycardia, atrioventricular block, uncompensated heart failure, and sick sinus syndrome, and must be used cautiously in patients with diabetes.

Newman W, McDermott B: Beta blockers for violence prophylaxis: case reports [letter]. *Journal of Clinical Psychopharmacology* 2011;31 (December):785–786. From the University of California Davis School of Medicine, Sacramento, Calif. **The authors declared no competing interests.**

Drug Trade Names: clonazepam—*Klonopin*, and others; fluphenazine decanoate—*Prolixin*, and others; pindolol—*Visken*, and others; propranolol—*Inderal*; quetiapine—*Seroquel*; trihexyphenidyl—*Artane*

Reference Guide

Odds Ratio: A comparison of the probability of an event in two 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 have been posted at www.alertpubs.com.

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