

PSYCHIATRY DRUG ALERTS

Antipsychotic-Associated Hypothermia	63
Brexipiprazole in Major Depression.....	61
Duloxetine Metabolism in Smokers	59
Estradiol in Schizophrenia	58
Minocycline in Schizophrenia	57
Reference Guide.....	64
Riluzole in Resistant Depression	62
Transdermal Treatments in Psychiatry.....	60

Volume XXXIII / August 2019 / Number 8

www.alertpubs.com

A new CME activity was recently released. Call us today to check your enrollment status.

Minocycline for Cognitive Deficits in Schizophrenia

In a randomized controlled trial in patients with schizophrenia, adjunctive minocycline (*Minocin*) produced significant improvements in cognitive function, some of which were correlated with changes in pro-inflammatory cytokines and negative symptom improvement.

Background: Antipsychotic medications have limited efficacy for cognitive deficits in schizophrenia, which may be related to microglia release of pro-inflammatory cytokines leading to immune-related disturbances and neuroinflammation. Minocycline has antiinflammatory effects and inhibits microglial activation.

Methods: Study subjects, aged 18–45 years, had a diagnosis of schizophrenia confirmed with structured clinical interview and a Positive and Negative Syndrome Scale (PANSS) negative symptom score of ≥ 20 . Participants were required to be free of antipsychotic medication for ≥ 2 weeks before study entry. Those with significant immune or inflammatory conditions or who had received antiinflammatories, immunosuppressants, or hormone therapy in the previous 6 months were excluded. Eligible patients received risperidone, flexibly dosed in the range of 3–6 mg/day plus double-blind, randomly assigned treatment with minocycline at 100 or 200 mg/day or placebo for 3 months. The primary outcome was cognitive function, measured with the MATRICS Consensus Cognitive Battery (MCCB). Interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) serum levels were also assessed in study patients and in 30 healthy controls.

Results: A total of 75 patients (mean age, 34 years; 29 men) received randomized treatment with 100 mg/day minocycline, 200 mg/day minocycline, or placebo (25 in each group). Of these, 57 completed the 3-month treatment protocol, with no between-group differences in completion rates. Drop outs were not related to adverse effects.

Cognitive function improved in all treatment groups with effect sizes* ranging from 0.14 to 0.45. At 3 months, the 200 mg/day minocycline group showed significantly greater improvement than the placebo group in scores on the trail making test and in verbal fluency ($p < 0.05$ for both). Improvements with 100 mg/day minocycline did not differ significantly from placebo. No serious adverse events were reported in any group.

PSYCHIATRY DRUG ALERTS (ISSN 2640-7620) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psych@alertpubs.com. © 2019 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Online subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157 institutional. Subscribers may enroll in the 12-month CME program for an additional \$83.00 per year, or enroll in the comprehensive, annual Self-Assessment program for \$270 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

At baseline and 3 months, serum levels of all inflammatory markers were significantly higher in patients with schizophrenia than in controls. After 3 months, patients in all treatment groups demonstrated significantly reduced levels of IL-1 β and IL-6 (effect sizes, 0.73 and 0.81, respectively). Improvements with 200 mg/day minocycline were significantly greater than with placebo ($p < 0.01$ for both); 100 mg/day minocycline did not differ from placebo. Serum TNF- α levels were not significantly reduced in any group. After adjustment for risperidone dosage and duration of illness, improvements in information processing speed, attention and vigilance, verbal and visual learning and memory, and working memory showed a significant correlation with decreases in IL-1 β and IL-6 in the 200 mg/day minocycline group ($p < 0.05$ and $p < 0.01$, respectively). Improvements in reasoning and problem solving were significantly correlated with decreases in IL-6 levels ($p < 0.05$). Improvements in verbal learning and memory were significantly associated with reductions in PANSS negative symptom score ($p = 0.033$).

Discussion: Previous studies of adjunctive minocycline in schizophrenia have had mixed results, with some indicating improved executive function, working memory, and attention and at least 1 study showing no significant differences in cognitive function between patients treated with minocycline and placebo. Although limited by small sample size and an ethnically heterogeneous population, the present results support the use of adjunctive minocycline to improve cognitive deficits and negative symptoms in patients with schizophrenia.

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

Zhang L, Zhang H, Wu R, Kosten T, et al: The effect of minocycline on amelioration of cognitive deficits and pro-inflammatory cytokines in patients with schizophrenia. *Schizophrenia Research* 2019; doi 10.1016/j.schres.2019.08.005. From the Second Xiangya Hospital, Hunan, China; and other institutions. **Funded by the National Key Research and Development Program; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Adjunctive Estradiol in Schizophrenia

In a placebo-controlled trial, adjunctive transdermal estradiol improved a range of symptoms in reproductive-aged women with severe schizophrenia.¹ However, treatment effects were limited to women aged >38 years suggesting that exogenous estrogen might be effective only when endogenous estrogen is beginning to decrease or when estrogen receptors become less sensitive in the menopausal transition.

Background: Research supports gender differences in the age of onset and course of schizophrenia, possibly indicating that estradiol could influence the course of the disease. A previous randomized controlled trial demonstrated that transdermal estradiol improved symptoms of schizophrenia in women of childbearing age.² The present study was undertaken to replicate those findings.

Methods: Study subjects were 200 women, aged 18–45 years, receiving either inpatient or outpatient treatment at a single psychiatric hospital. All women were receiving antipsychotic medication and had a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 60 . Postmenopausal women were excluded. Participants were randomly assigned to double-blind treatment with transdermal estradiol (200 mcg patches) or placebo. Patches were changed twice a week for 8 weeks. The primary outcome was change in PANSS positive symptom subscale score. Secondary outcomes included change in PANSS total, negative, and general psychopathology scores, as well as Clinical Global Impression–Severity (CGI–S) ratings, and Montgomery Asberg Depression Rating Scale (MADRS) scores.

Results: Study participants had a median age of 38 years and a median age at schizophrenia onset of 24 years; the mean PANSS positive symptom score was 19.6. Women in both the

estradiol and placebo groups experienced considerable symptomatic improvement during the study, with reductions in PANSS positive symptom score averaging 6 points in the estradiol group and 5.4-points in the placebo group (effect size,* 0.38; p=0.008). Secondary outcomes—the PANSS total score, negative symptoms, general psychopathology, CGI-S and MADRS scores—also favored the estradiol group, with most effect sizes in the medium range. When the analysis was stratified by age, improvements were limited to women aged >38 years. (See table.) Younger women did not show improvement. Neither type of background antipsychotic nor dosage affected outcomes. Adverse effects of estradiol were breast discomfort in 15 women and weight gain in 14.

Discussion: In this study the estradiol effect size was relatively large for an augmentation study in schizophrenia. The effect of the patch was driven by consistent improvement in a large number of symptoms. While it appears to be effective, long-term safety of estradiol is a concern, particularly for women with preexisting cardiovascular risks and those with a past or present diagnosis of breast cancer.

Effect Sizes for Estradiol Vs Placebo in Women Aged >38 Years		
Symptom Measure	Effect Size at Week 8	Significance
PANSS Positive	0.79	p<0.001
PANSS Negative	0.68	p<0.001
PANSS General	0.75	p<0.001
PANSS Total	0.83	p<0.001
CGI-S	0.51	p=0.007
MADRS	0.39	p<0.001

¹Weiser M, Levi L, Zamora D, Beigon A, et al: Effect of adjunctive estradiol on schizophrenia among women of child-bearing age: a randomized clinical trial. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1802. From Stanley Medical Research Institute, Kensington, MD; and other institutions. Funded by the Stanley Medical Research Institute. One of 14 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.

²Kulkarni J, et al: Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. *Molecular Psychiatry* 2015;20:695–702. doi 10.1038/mp.2014.33.

*See Reference Guide.

Duloxetine Metabolism in Smokers

Analysis of a therapeutic drug monitoring database found that despite receiving higher doses, patients who smoked cigarettes had significantly lower serum concentrations of duloxetine than nonsmokers.

Background: Although duloxetine metabolism is believed to be influenced by smoking, data on this relationship are scarce. Tobacco smoking induces CYP1A2, which metabolizes duloxetine, possibly reducing serum concentrations.

Methods: Study subjects were 125 inpatients receiving duloxetine treatment who had undergone routine therapeutic drug monitoring at a psychiatric hospital in Germany. Patients were allowed to smoke in special areas of this hospital, so there was little likelihood of the study results being influenced by smoking cessation. Subjects were excluded from the analysis if they were taking other drugs with CYP activity. Duloxetine serum concentrations were retrospectively compared between patients who smoked and those who did not.

Results: The analysis was based on 36 active smokers and 89 nonsmokers. On average, smokers received higher daily doses of duloxetine: 90 mg/day vs 60 mg/day in nonsmokers (p=0.001). However, serum concentrations were significantly lower in smokers (29.25 ng/mL

vs 47.5 ng/mL; $p=0.002$). The concentration-to-dose ratio was also significantly lower in smokers (0.325 vs. 0.7; $p<0.001$).

Discussion: The influence of smoking on some psychotropics (e.g., clozapine, fluvoxamine, mirtazapine, olanzapine) has been extensively studied. These results indicate smoking status affects duloxetine metabolism as well. Smoking status should be evaluated in patients who are prescribed the drug as smokers may require higher maintenance doses of duloxetine than nonsmokers. Dosage should be individualized because of the high interindividual variability of duloxetine metabolism. In addition, smoking cessation by a patient receiving a stable dose will likely be followed by a rapid and considerable increase in duloxetine concentrations. Therapeutic drug monitoring can be used to avoid adverse drug reactions in these patients.

Augustin M, Schoretsanitis G, Hiemke C, Grunder G, et al: Differences in duloxetine dosing strategies in smoking and nonsmoking patients: therapeutic drug monitoring uncovers the impact on drug metabolism. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.17m12086. From Aachen University, Germany; and other institutions. **This study was conducted without funding. Three of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: clozapine—*Clozaril*; duloxetine—*Cymbalta*; fluvoxamine—*Luvvox*; mirtazapine—*Remeron*; olanzapine—*Zyprexa*

Transdermal Treatments in Psychiatry

Several transdermal treatment options have received FDA approval for treatment of neuropsychiatric disorders including ADHD, depression, Parkinson's disease, and Alzheimer's disease, and others are used off-label. Additionally, transdermal formulations of drugs approved for the treatment of schizophrenia (i.e., aripiprazole, asenapine), are in development. Poor medication compliance in these patients makes the potential for use of transdermal systems particularly attractive, and while long-acting injectable formulations address the compliance issue, rapid reversal is not possible if the patient cannot tolerate the injected medication.

In a small placebo-controlled safety and bioavailability study in healthy adults, weekly transdermal aripiprazole provided sustained delivery of therapeutic doses over 7 days with no safety issues. A second study in healthy men, demonstrated that steady state was reached within 3 weeks of starting transdermal delivery, with concentrations similar to those found with oral aripiprazole. No safety signals were detected. According to the FDA, if bioequivalence can be established in a study comparing steady-state pharmacokinetics between aripiprazole transdermal and oral formulations, development of the formulation could be fast-tracked.

Asenapine, currently available only as a sublingual tablet, requires twice-daily dosing and has been associated with a metallic taste and oral hypoesthesia, as well as variability in plasma concentrations due to alterations in absorption. Furthermore, bioavailability is negligible if asenapine is swallowed rather than allowed to orally disintegrate and be absorbed via the oral mucosa. A recently completed phase 3 controlled trial of high- and low-dose transdermal asenapine patches (equivalent to 10 mg and 5 mg twice daily sublingual asenapine, respectively) indicated the patches were effective in adults experiencing an acute exacerbation of schizophrenia. The safety profile of transdermal asenapine was consistent with the sublingual formulation, and no deaths or serious adverse events were reported in the 6-week study.

Advantages of transdermal delivery may include improved patient and caretaker satisfaction based on ease of use, improved adherence due to reduced dosing frequency, improved tolerability that could result from avoidance of the hepatic first-pass metabolism allowing for lower therapeutic doses and causing fewer adverse effects and drug interactions. In addition, there is

a potential for reduced risk of overdose or abuse with transdermal delivery as patch removal stops drug delivery. Furthermore, once steady-state concentrations of the drug are reached, plasma concentrations remain stable while the patch is worn, thus avoiding episodic peaks and troughs that occur with oral formulations. However, largely due to the difficulties associated with crossing the outermost layer of the skin, only about 1% of FDA-approved drugs are available for transdermal delivery in the U.S. (See table.)

Transdermal Drug Treatments for Neuropsychiatric Diseases		
Drug Name	FDA-Approved Indication	Off-Label Uses
Scopolamine	Motion sickness	Clozapine-associated sialorrhea
Clonidine	Hypertension	ADHD, oppositional-defiant disorder, PTSD, Tourette’s syndrome, impulse control disorders in autism
Nicotine	Smoking cessation	ADHD, depression
Estrogen	Menopausal symptoms, prevention of postmenopausal osteoporosis	Premenstrual dysphoric disorder, postpartum depression
Testosterone	Hypogonadism, delayed puberty, palliative treatment of breast cancer	Depression (particularly in men with hypogonadism or advanced age), female hypoactive sexual desire disorder
Methylphenidate	ADHD (children and adolescents)	Adult ADHD, depression
Selegiline	Depression (adult)	—
Rotigotine	Parkinson’s disease	—
Rivastigmine	Dementia	—

Citrome L, Zeni C, Correll C: Patches: established and emerging transdermal treatments in psychiatry. *Journal of Clinical Psychiatry* 2019;80(4):18nr12554; doi 10.4088/JCP.18nr12554. From New York Medical College, Valhalla; and other institutions. Funded by Noven Pharmaceuticals. All study authors disclosed potentially relevant financial relationships with commercial sources, including Noven Pharmaceuticals.

Common Drug Trade Names: aripiprazole—*Abilify*; asenapine—*Saphris*; clonidine, transdermal—*Catapres-TS*; estrogen, transdermal—*Alora, Climara*; methylphenidate, transdermal—*Daytrana*; nicotine, transdermal—*NicoDerm CQ*; rivastigmine, transdermal—*Exelon*; rotigotine, transdermal—*Neupro*; selegiline, transdermal—*Emsam*; scopolamine, transdermal—*Transderm Scop*; testosterone, transdermal—*Androderm*

Adjunctive Brexpiprazole in MDD

Safety and efficacy of adjunctive brexpiprazole in depression have been demonstrated in short-term studies, but long-term treatment is recommended to prevent relapse. In a multi-center, manufacturer-sponsored, open-label study, adjunctive treatment with brexpiprazole (*Rexulti*) was both safe and well tolerated for up to 6 months in patients with treatment-resistant major depression.

Methods: Study subjects were rolled over into the present study following completion of 1 of 3 prior randomized controlled trials of brexpiprazole in treatment-resistant depression. Regardless of brexpiprazole exposure in the parent study, all participants received open-label treatment titrated in the range of 0.5–3 mg/day in addition to their background SSRI or SNRI, which remained unchanged. The study duration was planned for 52 weeks, but a midpoint analysis demonstrated a well-established safety profile, and the protocol was amended to

reduce the duration to 26 weeks. As the primary outcome, safety was determined via assessment of treatment-emergent adverse events, clinical laboratory tests, and physical examination. Extrapyramidal symptoms (EPS), suicidality, and sexual function were formally assessed using validated scales. Efficacy was also assessed.

Results: A total of 2944 patients (mean age, 45 years; 68% women) were enrolled, and >2100 received adjunctive brexpiprazole for ≥ 6 months. Nearly three-quarters of patients experienced ≥ 1 treatment-emergent adverse effect, and 253 patients (9%) discontinued brexpiprazole treatment because of them. The most frequently reported adverse effects included weight gain (18%); somnolence (8%); headache and akathisia (7% each); increased appetite, insomnia and fatigue (6% each); and anxiety (5%). The mean increase in weight after 26 weeks of treatment was 6 lbs, and treatment-emergent metabolic syndrome was identified in 3% of patients. There were no clinically relevant changes in prolactin, lipid, or glucose levels. A total of 4 patients died during the study period; 1 by suicide that was judged to be possibly related to brexpiprazole treatment. Participants reported improved sexual function and demonstrated improvement on all efficacy measures and functional outcomes. Clinical Global Impression–Severity scores showed continued improvement of on average 1.1 points over initial improvement in the parent studies.

Discussion: Atypical antipsychotics are often used as adjuncts to antidepressants in patients with resistant depression. Common adverse effects of these medications include akathisia, sedation, metabolic abnormalities, and prolactin increases, which are linked to sexual dysfunction. The present results suggest that with adjunctive brexpiprazole, the incidence of akathisia and sedation are low, and changes in laboratory values are unremarkable, and there are no clinically relevant adverse effects on sexual function. No unexpected safety signals emerged, and the tolerability profile was similar to that of short-term brexpiprazole treatment.

Hobart M, Zhang P, Skuban A, Brewer C, et al: A long-term, open-label study to evaluate the safety and tolerability of brexpiprazole as adjunctive therapy in adults with major depressive disorder. *Journal of Clinical Psychopharmacology* 2019;39 (May/June):203–209. From Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ; and H. Lundbeck A/S, Denmark. **Funded by Otsuka; and H. Lundbeck. All study authors disclosed financial relationships with Otsuka or H. Lundbeck.**

Adjunctive Riluzole in Resistant Depression

Results of an open-label extension study suggest that 12 weeks of adjunctive riluzole is well tolerated and improves outcomes in patients with treatment-resistant unipolar depression.¹

Background: The glutamate inhibitor riluzole, FDA approved for treatment of amyotrophic lateral sclerosis, is believed to work by inhibiting presynaptic glutamate release. The agent has shown promise in open-label studies of treatment-resistant mood disorders, but double-blind controlled trials of adjunctive riluzole in resistant depression have had mixed results. However, study durations were short (4–8 weeks) and the efficacy of longer-term treatment has not previously been investigated. The present study examined the longer-term efficacy of adjunctive riluzole in an open-label extension phase of a multicenter acute-phase trial that did not support the efficacy of riluzole at 8 weeks.²

Methods: Study participants entered the extension phase following 8 weeks of double-blind randomized treatment with riluzole or placebo added to a background SSRI, SNRI, or bupropion. For entry in the parent study, patients were required to be aged 18–65 years, to be experiencing at least moderate depression despite ≥ 1 but ≤ 4 adequate antidepressant trials, and to have a Montgomery Asberg Depression Rating Scale (MADRS) score of ≥ 28 . Those with bipolar disorder or psychotic depression or at serious risk of suicide were excluded. Of 85 eligible patients, 66 entered the extension phase during which all patients received adjunctive treatment with 50 mg riluzole b.i.d. The primary outcome was response, defined as a ≥ 50 decrease in MADRS score, after 12 weeks of open-label treatment.

Results: The 66 extension-phase participants were on average in their late 40s, and 31 were women. For the primary analysis of response, participants were divided into 4 groups based on acute-phase treatment and response status. Among the 12 patients who met acute-phase response criteria with either riluzole or placebo, 8 (67%) maintained their response at the end of the extension phase. In the group who did not achieve response with acute treatment (n=54), a total of 13 (24%)

achieved response following the 12-week extension. (See table.) An additional 8 patients (15%) demonstrated a $\geq 25\%$ reduction in MADRS score. Within the acute response and nonresponse groups, outcomes did not differ significantly based on initial treatment with riluzole or placebo. In addition, no statistically significant differences were found on any of the secondary outcome measures (e.g., MADRS reductions, Clinical Global Impression Ratings, and self-rated depression symptoms).

Outcomes by Acute Phase Treatment Assignment	
Acute Phase Assignment/Outcome	Extension Phase Response Rate
Riluzole Responders (n=7)	71.4%
Placebo Responders (n=5)	60%
Riluzole Nonresponders (n=30)	20%
Placebo Nonresponders (n=24)	29.2%

Riluzole was well tolerated. The most commonly reported adverse events were fatigue (9%), vivid dreams or nightmares (6%), nausea (6%), and nasal congestion (6%). One patient discontinued treatment due to vomiting and global amnesia, judged to be probably related to riluzole. No significant liver function abnormalities were discovered.

Discussion: Although the results appear to be positive, because the efficacy was analyzed in an open-label extension of a placebo-controlled trial, potential placebo effects cannot be ruled out. Additionally, the sample size was small, particularly the group of acute phase responders, which limits our power to detect between-group differences. Additional study of adjunctive riluzole in treatment-resistant depression appears to be warranted.

¹Sakurai H, Dording C, Yeung A, Foster S, et al: Longer-term open-label study of adjunctive riluzole in treatment-resistant depression. *Journal of Affective Disorders* 2019; doi 10.1016/j.jad.2019.06.065. From Massachusetts General Hospital, Boston; and other institutions. **Funded by NIMH; and other sources. Seven of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Mathew S, et al: A randomized, double-blind, placebo-controlled, sequential parallel comparison design trial of adjunctive riluzole for treatment-resistant major depressive disorder. *Neuropsychopharmacology* 2017; 42:2567–2574; doi 10.1038/npp.2017.106.

Common Drug Trade Names: bupropion—*Wellbutrin*; riluzole—*Rilutek*

Antipsychotic-Associated Hypothermia

Hypothermia is a rare but potentially fatal adverse effect of antipsychotic drug use. While few cases have been reported in the literature, a previous review found evidence of its occurrence with haloperidol, clozapine, risperidone, and olanzapine. A review of 5 subsequent cases of antipsychotic-associated hypothermia provides additional information on the adverse effect as well as potentially predisposing factors.

The 5 patients (3 men) ranged in age from 27 to 77 years and experienced mild or moderate hypothermia judged to be possibly related to their antipsychotic treatment for schizophrenia or schizoaffective disorder. (See table, next page.) Of the 5 patients, 4 were nursing home residents or long-term inpatients at a single facility. The remaining patient (27-year-old male) was homeless, but brought to the facility for hypothermia treatment. With gradual rewarming, body temperature normalized within a few hours in 4 of the patients. The final patient also required several medication changes over the course of 5 days before her temperature normalized. Two

patients experienced subsequent occurrences of hypothermia. Patient #1 had 3 additional episodes over 2 years with the same medication and after a medication change, and patient #3 had a single recurrence with the same medication regimen after 4 months.

Characteristics of Patients with Antipsychotic-Associated Hypothermia					
	Gender	Age	Medication	Treatment	Predisposing Factors
1	Male	74 years	Depot zuclopenthixol	Rewarming	Advanced age
2	Male	27 years	Depot penfluridol	Rewarming	Cold exposure/ homelessness; illicit substance use
3	Female	77 years	Haloperidol, lorazepam	Rewarming	Advanced age, subclinical hypothyroidism, polypharmacy
4	Male	65 years	Clozapine	Rewarming	Advanced age, recent dosage increase, history of hypothyroidism
5	Female	59 years	Clozapine, risperidone, olanzapine, lorazepam	Rewarming, olanzapine and clozapine discontinued, risperidone dosage decreased	Polypharmacy, recent dosage increase, laboratory evidence of infection

Although the pathophysiological mechanism of antipsychotic-associated hypothermia is unclear, it may be related to peripheral vasodilatation and a failure of central thermoregulation. The present case reports in combination with the previous review suggest that advanced age, recent drug initiation or dosage increase, and presence of hypothyroidism may be predisposing factors for antipsychotic-related hypothermia.

Zonnenberg C, Bueno-de-Mesquita J, Ramlal D, Blom J: Antipsychotic-related hypothermia: five new cases. *Frontiers in Psychiatry* 2019; doi 10.3389/fpsy.2019.00543. From Parnassus Psychiatric Institute, The Netherlands. **The authors did not include disclosure of potentially relevant financial relationships.**

Common Drug Trade Names: clozapine—*Clozaril*; haloperidol—*Haldol*; lorazepam—*Ativan*; olanzapine—*Zyprexa*; penfluridol, depot (not available in the U.S.)—*Semap*; risperidone—*Risperdal*; zuclopenthixol, depot (not available in the U.S.)—*Clopixol*

Reference Guide

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.

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.

Contributing Editors: **Kate Casano, MSHyg; Bennett Silver, MD**

Consulting Editor: **Steven J. Schleifer, MD**, Rutgers–New Jersey Medical School

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann** Assistant Editor: **Donna Foehner**

Founding Editor: **Michael J. Powers**

Off-Label Drug Use Statement: Some drugs discussed for specific indications in *Psychiatry Drug Alerts* articles may not be approved for labeling and advertising for those indications by the United States FDA.
