Risperidone Recall

A recall has been issued by Ortho-McNeil-Janssen Pharmaceuticals for specific lots of 3-mg Risperdal (risperidone) tablets and 2-mg generic risperidone tablets because of an uncharacteristic musty odor thought to come from trace amounts of 2,4,6-tribromoanisole (TBA), the metabolite of a chemical fungicide used to treat wooden pallets on which the products are stored. McNeil Consumer Health has also recalled one lot of over-the-counter Tylenol Extra Strength caplets (225 count) for the same musty odor. TBA is not believed to be toxic, but it has been associated with transient GI symptoms. Several months ago, a similar recall was issued by Ortho-McNeil Neurologics for specific lots of topiramate (Topamax).

Low-Dose Antipsychotics for Relapse Prevention

According to a meta-analysis, low-dose antipsychotic therapy is as effective as standard-dose therapy in preventing relapse of schizophrenia. However, very low-dose therapy (i.e., less than half the standard dose) is not.

Methods: All published, randomized, double-blind clinical trials that included ≥2 dosage groups of the same antipsychotic were reviewed. Included studies (n=13; 1395 patients) were carried out in clinically stable patients with schizophrenia or schizoaffective disorder and had a minimum follow-up of 24 weeks. All but 2 trials included ≥1 year of follow-up. Second-generation antipsychotics were evaluated in 4 of the studies. Depot administration was used in 1 study of second-generation agents and in 7 studies of older drugs. Standard dosage was defined as a minimum of the World Health Organization’s Defined Daily Dose (DDD) for each agent. Low
dosage was defined as half to <100% of the DDD, and very low dosage as less than half the DDD. The primary study outcome was treatment failure, defined as premature discontinuation of assigned treatment for any reason. Psychiatric hospitalization was a secondary outcome.

**Results:** Rates of treatment failure did not differ between standard and low drug doses (risk difference, 0.02; 95% confidence interval,* 0.05–0.10). Very-low-dose therapy was inferior to both low- and standard-dose therapy, with a number needed to harm* (NNH) of 8. Patterns were similar for rates of hospitalization and clinical relapse, which also did not differ between standard- and low-dose therapy, but were superior to very-low-dose therapy (NNH 9 and 4, respectively). Rates of discontinuation for adverse effects were similar in all 3 groups.

**Discussion:** Major treatment guidelines differ in their recommendations on antipsychotic maintenance dosing. The American Psychiatric Association and the Schizophrenia Patient Outcomes Research Team (PORT) recommend the lowest possible dosage, but the Expert Consensus Guidelines recommend continuing the same dosage that was effective in acute treatment. It should be noted that the Expert Consensus Guidelines are based heavily on studies conducted in the 1980s comparing standard and very low dosages.

The authors note a lack of clinical trial data on appropriate maintenance dosing, especially for the newer agents. Nonetheless, they conclude that standard and low dosages are equally effective, while very low dosages are not effective. Therefore, they suggest that a moderately low maintenance dosage should be the optimal target in clinical practice.

**Study Rating*—16 (89%):** This study met all criteria for a meta-analysis, except that individual study quality was not assessed.

Uchida H, Suzuki T, Takeuchi H, Arenovich T, et al: Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Schizophrenia Bulletin 2011;37 (July):788–799. From Keio University School of Medicine, Tokyo, Japan; and other institutions. The study was conducted without funding. Several study authors disclosed financial relationships with commercial sources.

*Drug Trade Names: fluphenazine decanoate—Prolixin decanoate; haloperidol decanoate—Haldol decanoate; olanzapine—Zyprexa; pimozide—Orap; risperidone, long-acting—Risperdal Consta; quetiapine—Seroquel; ziprasidone—Geodon

*See Reference Guide.

**Discontinuing Antipsychotic Polypharmacy**

In a multisite randomized trial, patients who switched from antipsychotic polypharmacy to monotherapy were less likely to continue their assigned treatment than those who continued to receive polypharmacy.\(^1\) However, the switch was not associated with differences in symptoms or in most adverse effects.

**Methods:** Study participants (n=114) were patients with schizophrenia or schizoaffective disorder, who were being treated at either a NIMH Schizophrenia Trials Network site or in the Connecticut public mental-health system. All received a 2-drug combination that did not include clozapine. Patients were required to have detectable plasma levels of both drugs, as well as persistent psychopathology or adverse effects. Participants were randomly assigned to either continue both prescribed antipsychotics or to discontinue 1 of them. Physicians and

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>WHO Defined Daily Dose for Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Long-acting risperidone</td>
<td>1.8 mg (25.2 mg/2 weeks)</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>3.3 mg (92.4 mg/4 weeks)</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>1 mg (14 mg/ 2 weeks)</td>
</tr>
<tr>
<td>Pimozide</td>
<td>4 mg</td>
</tr>
</tbody>
</table>
patients decided together which of the 2 drugs would be discontinued, and medication dosages were adjusted according to clinical judgment. Treatment was not blinded, but study outcomes were rated by blinded observers. The primary outcome was discontinuation of assigned medication for any cause. Patients were observed for 6 months of assigned treatment and then for another 6 months of naturalistic follow-up.

**Results:** The most common antipsychotic combinations at baseline were quetiapine plus risperidone, and quetiapine, risperidone, or olanzapine plus a first-generation agent, each accounting for about one-fifth of participants. Among those whose baseline treatment included a first- and second-generation agent and who were assigned to the discontinuation group, second-generation agents were continued slightly more often (55%) than first-generation ones.

Of the 58 patients in the monotherapy group, 15 returned to polypharmacy (12 with the same combination), 2 switched to another single agent, and 1 began, but did not complete, a taper of 1 medication. Reasons for discontinuation of monotherapy included increased symptoms in 11 patients, patient preference in 6, and adverse effects in 1. In the polypharmacy group, 8 patients discontinued their assigned treatment for various reasons. After 6 months, 86% of patients assigned to continued polypharmacy remained on the same medication regimen, compared with 69% of those assigned to the monotherapy group (p=0.03). Time to medication change was significantly shorter for patients who remained on polypharmacy than for those who switched to monotherapy.

Neither group experienced a significant change in psychopathology, measured using the Positive and Negative Syndrome Scale, during the randomized treatment period. In addition, the incidence of new-onset extrapyramidal symptoms (29–30%), tardive dyskinesia (19%), and psychiatric hospitalization (8–11%) was comparable in the groups. Average body mass index increased by 0.28 points in the polypharmacy group and decreased by 0.5 points in the patients who switched to monotherapy.

**Discussion:** Polypharmacy, although common in patients with schizophrenia (currently estimated at 30–40% of patients), is supported by little evidence. In this study, switching to monotherapy was accomplished successfully nearly 70% of the time, but was associated with a higher level of dissatisfaction that often resulted in patients returning to their prior 2-drug regimen. There was little difference in clinical effects. These results support prescribing guidelines that recommend trials of antipsychotic monotherapy in patients receiving >1 agent, provided the patient can return to polypharmacy if the single agent produces unsatisfactory results.

According to the accompanying editorial, there is a rationale and evidence supporting the combination of antipsychotics with differing mechanisms of action. However, clozapine is the only antipsychotic that acts via a different mechanism, and the present study excluded patients prescribed regimens with clozapine. Concerns about combining agents with similar actions, particularly increased risk of adverse effects, were not supported by these study results. Although monotherapy, when effective and well tolerated, is optimal, combining agents may be preferred for some patients after other options have failed.

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

1 Essock S, Schooler N, Stroup T, McEvoy J; et al: Effectiveness of switching from antipsychotic polypharmacy to monotherapy. *American Journal of Psychiatry* 2011;168 (July):702–708. From the New York State Psychiatric Institute, New York; and other institutions. **Funded by the NIMH.** Several study authors disclosed financial relationships with commercial sources.

2 Goff D, Dixon L: Antipsychotic polypharmacy: are two ever better than one [editorial]? *American Journal of Psychiatry* 2011;168 (June):667–669. From Harvard Medical School at Massachusetts General Hospital, Boston. **Both authors disclosed financial relationships with commercial interests.**

**Drug Trade Names:** clozapine—**Clozaril**; olanzapine—**Zyprexa**; quetiapine—**Seroquel**; risperidone—**Risperdal**

*See Reference Guide.*
Moderators of Lisdexamfetamine Effects in Adult ADHD

In adults with ADHD, baseline symptom severity, previous ADHD treatment, and level of inattentive symptoms do not appear to affect the dose-response relationship of lisdexamfetamine dimesylate (Vyvanse). However, higher doses may be more effective in patients with more severe hyperactive-impulsive symptoms.

**Background:** Lisdexamfetamine is a long-acting prodrug stimulant approved for treatment of ADHD in adults and children. Following ingestion, it is converted to active D-amphetamine. Efficacy in adults is dose-related and comparable to other stimulant medications.

**Methods:** The present study is a secondary analysis of previously published data from a 4-week placebo-controlled trial of 3 daily doses of lisdexamfetamine: 30, 50, and 70 mg. Participants were 420 adults with ADHD. The analysis was conducted to determine whether the known relationship of dose to clinical response was moderated by baseline illness severity, prior pharmacotherapy, or ADHD symptom type.

**Results:** Baseline lisdexamfetamine dose was significantly predictive of final scores on the ADHD Rating Scale (p<0.001), the primary outcome of the efficacy study. For all doses, effect sizes were greater in patients with greater baseline severity of ADHD. However, those who were the most severely ill at baseline remained the most severely ill following treatment. The lack of interaction between the dose-response effect and baseline severity indicates that there is no evidence patients with more severe illness require higher doses or that those with less severe illness require lower doses.

The dose-response relationship was not affected by prior stimulant therapy or by the baseline level of inattentive symptoms. The effect was modified by the level of baseline hyperactive/impulsive symptoms, with higher doses showing significantly greater benefit (p≤0.002) in patients with more severe symptoms.

Faraone S, Spencer T, Kollins S, Glatt S, et al: Dose response effects of lisdexamfetamine dimesylate treatment in adults with ADHD: an exploratory study. *Journal of Attention Disorders* 2011; doi 10.1177/1087054711403716. From SUNY Upstate Medical University, Syracuse, N.Y.; and other institutions. **Funded by Shire. All study authors disclosed financial relationships with Shire, manufacturer of Vyvanse, and other commercial sources.**

Dronabinol Improved Trichotillomania

In a pilot study, the cannabinoid agonist dronabinol reduced hair pulling by an average of nearly 50% in a group of women with trichotillomania.

**Background:** There are currently no medications FDA approved to treat trichotillomania, but controlled trials have suggested efficacy for N-acetyl cysteine; clomipramine; olanzapine; and psychosocial treatments (e.g., cognitive-behavioral therapy). Glutamatergic dysfunction has been suggested as an underlying factor in trichotillomania. Because dronabinol targets excessive glutamatergic drive, it was investigated in an open-label trial.

**Methods:** Study subjects were 14 patients (all female; mean age, 33 years) with a primary diagnosis of trichotillomania who were recruited via advertisement or referred for medication treatment. Psychiatric comorbidity other than bipolar disorder, suicidality, psychosis, and substance abuse were not exclusionary, and patients were permitted other psychotropic medication provided it had been stable for ≥3 months. Participants received flexibly dosed dronabinol, initiated at 2.5 mg/day and titrated to a maximum of 15 mg/day, for 12 weeks. The Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) was administered at baseline and repeated at 3-week intervals. Because dronabinol contains THC, which has been linked to cognitive deficits, cognitive function was assessed at baseline and study end.
Results: The mean MGH-HPS score decreased by almost 50% with dronabinol treatment: from 17 at baseline to 9 at 12 weeks (p=0.001). Nine patients (64%) were judged to be responders with a ≥35% decrease in MGH-HPS score and a rating of “much improved” or “very much improved” on the Clinical Global Impression-Improvement scale. Treatment response occurred across the dosage range. Clinical and demographic variables and concomitant medication use did not appear to affect response. Treatment did not affect any of the cognitive measures.

Two of the 14 patients (14%) withdrew from the study because they were unable to comply with the study schedule. The remaining 12 patients completed the protocol. Adverse effects included lightheadedness/dizziness (n=4); a “high” sensation (n=3); sedation and constipation (n=2 each); and headache and nausea/vomiting (n=1 each). These were mild to moderate and resolved without sequelae.

Discussion: This appears to be the first study to examine a cannabinoid agonist in trichotillomania. Although the study was limited by the small sample and open-label design, the results suggest that modulating the cannabinoid system with dronabinol may significantly reduce the compulsive motor aspects of trichotillomania without producing THC-associated cognitive deficits. The authors caution that dronabinol, approved for AIDS-related anorexia and weight loss and cancer-related nausea/vomiting, is a schedule-3 controlled substance and has the potential to be habit forming. It should be used with caution in patients with a history of substance addiction. In addition, ethical implications of treating non-life-threatening disease with a potentially habit-forming substance should be considered.

Grant J, Odlaug B, Chamberlain S, Kim S: Dronabinol, a cannabinoid agonist, reduces hair pulling in trichotillomania: a pilot study. Psychopharmacology 2011; doi 10.1007/s00213-011-2347-8. From the University of Minnesota School of Medicine, Minneapolis. Funded by University of Minnesota research funds. The study authors disclosed financial relationships with commercial sources.

Drug Trade Names: dronabinol—Marinol; clomipramine—Anafranil; olanzapine—Zyprexa

SSRIs: Long-Term Results in Hypochondriasis

Hypochondriasis is considered a chronic condition with a low remission rate. SSRIs have been shown to be effective in acute treatment, but long-term data is lacking. In a follow-up study, the majority of patients with hypochondriasis who received SSRI therapy achieved long-term remission. Continued SSRI therapy was an important predictor of outcome.

Methods: Patients (n=58) who had participated in 1 of 2 clinical trials of SSRIs in hypochondriasis were eligible for study. Acute SSRI response rates in the studies (1 of open-label fluvoxamine; 1 controlled trial of fluoxetine) were 57–63%. Patient contact was not maintained and treatment was not dictated by the study protocol after completion of the 12 week trials. Follow-up interviews were conducted by phone or in person with 45 of the 58 patients (78%) a mean of 9 years (range, 4–16 years) later. Remission during follow-up was defined as no longer meeting full DSM-IV criteria for hypochondriasis.

Results: At their follow-up interview, 27 patients (60%) no longer met DSM-IV criteria for hypochondriasis. Of these, 20 patients had used an SSRI for at least 1 month at some time during follow-up; 11 were still using one when the interview was conducted. There was no significant difference in baseline symptom severity between these patients and those who did not use an SSRI during follow-up. The most commonly used SSRIs were fluoxetine, escitalopram, and fluvoxamine. Factors predictive of lower likelihood of response were lack of SSRI use, duration of hypochondriasis before treatment (odds ratio* for nonresponse, 1.17; p=0.003), and history of childhood punishment by hitting (odds ratio, 11; p=0.01). Lack of response in the initial study was not a significant predictor of nonresponse during follow-up.
Discussion: The long-term prognosis of hypochondriasis may be better than previous reports suggest. In earlier studies, two-thirds of patients remained ill after 4–5 years. The authors attribute the favorable outcomes in their patients to the high use of SSRIs. The other findings suggest the importance of treating early in the disease course and addressing childhood traumatic events.


*Drug Trade Names*: escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox

*Lurasidone Efficacy*

In a multicenter controlled trial, lurasidone (Latuda), a recently introduced antipsychotic, was effective in patients with acute exacerbation of chronic schizophrenia. The agent was associated with relatively few metabolic effects and modest increases in prolactin.

**Methods:** Study participants were 478 adults with schizophrenia of at least 1 year in duration who were hospitalized within the prior 2 weeks for an acute episode. Participants were required to have a Clinical Global Impression Severity* (CGI-S) score of ≥4 and a Positive and Negative Syndrome Scale (PANSS) total score of ≥80, indicating at least moderate illness severity. They were randomly assigned to 6 weeks of treatment with double-blind lurasidone at 40 mg or 120 mg/day, placebo, or 15 mg/day olanzapine. The olanzapine arm was included to test for assay sensitivity, and direct efficacy comparisons between the lurasidone and olanzapine groups were not a principal result. Primary outcome measures were the PANSS and the CGI-S scores.

**Results:** The proportion of patients completing treatment was comparable in the olanzapine, placebo, and 40-mg lurasidone groups (61–68%) and somewhat lower for 120 mg lurasidone (56%). Changes in PANSS total score were significantly greater (p=0.002) in the 2 lurasidone groups than in the placebo group. (See table.) The average CGI-S score decreased by 1.4–1.5 points in the active treatment groups and by 1.1 point in the placebo group (p≤0.04). For both efficacy outcomes (CGI-S and PANSS total scores), the 2 lurasidone doses and olanzapine were statistically equivalent at 6 weeks. Olanzapine, but not lurasidone, was associated with significant improvement in depressive symptoms as rated on the Montgomery-Asberg Depression Rating Scale (MADRS), but baseline scores in all groups were low (mean, 11).

<table>
<thead>
<tr>
<th></th>
<th>40 mg lurasidone</th>
<th>120 mg lurasidone</th>
<th>Olanzapine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Endpoint</td>
<td>Baseline</td>
<td>Endpoint</td>
</tr>
<tr>
<td>PANSS total</td>
<td>97</td>
<td>71</td>
<td>98</td>
<td>74</td>
</tr>
<tr>
<td>CGI-S</td>
<td>5</td>
<td>3.5</td>
<td>5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Adverse event rates were similar in the 40-mg lurasidone and placebo groups and somewhat higher with 120 mg lurasidone and olanzapine. The events with the highest incidence in lurasidone-treated patients (relative to placebo) were akathisia, agitation, nausea, and...
parkinsonism and, at the higher dose, somnolence and sedation. Anticholinergic medication was prescribed in 20% of the lower-dose lurasidone group and in 41% of the higher-dose group.

In contrast to olanzapine, treatment with lurasidone was not associated with changes in weight, body mass index, or lipid levels, relative to placebo. Elevations in prolactin were observed in 13% of men and 20% of women treated with lurasidone, similar proportions to the olanzapine group. There were no lurasidone-related ECG abnormalities.

**Discussion:** Results of this study support the FDA’s recommended lurasidone dosage range of 40–80 mg/day.

**Study Rating**—15 (88%): This study met most criteria for a randomized controlled trial, but the source of funding was not stated.


*Drug Trade Names:* lurasidone—**Latuda**; olanzapine—**Zyprexa**

*See Reference Guide.*

### Nocturnal Enuresis with Atypical Antipsychotics

Results of an observational study indicate that nocturnal enuresis is a common adverse effect of atypical antipsychotic treatment, with a prevalence that varies by agent. The rate was higher with clozapine (1 in 5 patients) than with other atypsicals.

**Methods:** Study subjects were patients, aged 15–64 years, living in a single urban area of New Zealand to whom clozapine, olanzapine, quetiapine, or risperidone was dispensed during a 4-month period. A routine physician questionnaire used to assess postmarketing drug safety included specific questions about treatment-emergent nocturnal enuresis and daytime urinary leakage. Psychiatrists, mental health nurses, and general practitioners were asked to complete the questionnaire for patients taking one of the antipsychotics. A total of 606 patients were included in the analysis. Risperidone accounted for 42% of antipsychotic use, followed by olanzapine (22.5%), quetiapine (21%), and then clozapine (14%). Thirty-six patients contributed data for >1 agent.

**Results:** A total of 41 patients (7%) experienced onset of nocturnal enuresis after they began taking an antipsychotic. This rate is substantially higher than the estimated background incidence of 0.5% in noninstitutionalized adults. Compared with the other atypsicals, the incidence was significantly greater with clozapine (21% vs 6–10%; see table). There were no significant differences among olanzapine, quetiapine, and risperidone. Risk of enuresis was associated

<table>
<thead>
<tr>
<th></th>
<th>% of Patients Reporting Enuresis</th>
<th>Odds Ratio* (adjusted for age, gender, duration of treatment)</th>
<th>95% Confidence Interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>21</td>
<td>1 (reference group)</td>
<td>N/A</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10</td>
<td>0.43</td>
<td>0.19–0.96</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>7</td>
<td>0.33</td>
<td>0.13–0.59</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6</td>
<td>0.27</td>
<td>0.12–0.59</td>
</tr>
</tbody>
</table>
with a childhood history of bedwetting and with concomitant use of >1 antipsychotic, but not with use of other concomitant CNS medications.

**Discussion:** The authors note that nocturnal enuresis is often unreported by patients. An important strength of the present study is that patients were directly questioned by their physician about bedwetting. Because antipsychotic-associated nocturnal enuresis appears to be more common than previously believed and it may jeopardize medication compliance, patients taking atypicals should be directly questioned about its occurrence. Although the causal mechanism of antipsychotic-associated enuresis is unclear, it may be the related to the drugs’ anticholinergic and antiadrenergic effects on muscles that control urination. Management may include drug treatments, antipsychotic dose reduction, and limiting fluid intake plus complete bladder emptying before going to bed.


*Drug Trade Names:* clozapine—*Clozaril*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*

*See Reference Guide.*

**Reference Guide**

**Confidence Interval:** The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

**Clinical Global Impression Severity Scale:** A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

**Number Needed to Harm:** A measure of how many patients need to be exposed to a risk factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

**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.