Olanzapine-Associated Restless Leg Syndrome

Psychotropic-associated restless leg syndrome (RLS) is widely recognized. There have been reports with clozapine, risperidone, and mirtazapine and with several antidepressants. There have also been 2 reports in the literature of olanzapine-associated RLS, and 3 new patients have been described. The patients (2 males, 1 female; aged 29–62 years) were treated with 2.5–15 mg/day olanzapine for schizophrenia or bipolar disorder. Within days of starting treatment or a dosage increase they experienced unpleasant sensations including burning, twitching, and paresthesia that were relieved only by walking or moving. All 3 patients reported the symptoms occurred only at rest, worsened at night, and interfered with sleep. The addition of lorazepam (for presumed akathisia) in 1 patient was not helpful. The symptoms resolved when patients stopped taking olanzapine, and recurred with rechallenge in the 1 patient who consented to try it. Symptoms did not re-emerge with alternate antipsychotic treatment in any of the patients.


Drug Trade Names: clozapine—Clozaril; lorazepam—Ativan, and others; mirtazapine—Remeron; olanzapine—Zyprexa; risperidone—Risperdal

Antidepressants and Suicide—Advancing Knowledge

Previous analyses of antidepressant-related suicide generally evaluated risk associated with any antidepressant use and did not study risk with individual agents. A new cohort study found no clinically meaningful differences in risk between antidepressant classes or individual drugs.

Background: The FDA warning on suicide with antidepressants was based on a meta-analysis of studies with important limitations such as short trial durations, few suicide attempts and no completed suicides, nonstandardized definitions of suicidality, dosing variations, and heterogeneous patient populations. Nonrandomized studies comparing antidepressant classes have shown some small differences in suicides and suicide attempts, but these may have been under-
powered or affected by prescribing bias. It has also been suggested that SSRIs increase the risk of violent suicide, but this was not supported in a postmortem study. The present study addressed "whether the risk of suicide is equal across antidepressant classes and agents after adjustment for selection factors—or whether there are particular regimens with safety advantages that should be prescribed preferentially in adult populations."

**Methods:** A cohort of Canadian residents aged ≥18 years (n=287,543) who started antidepressant therapy for depression between 1997 and 2005 were identified from a national pharmacy database. Nearly 70% of the patients were treatment-naïve, not having received antidepressants in the previous 3 years. Antidepressants were classified as SSRIs, SNRIs, TCAs, MAOIs, and other. Agents not included in the analysis were bupropion, because of its potential use for smoking cessation, and escitalopram and duloxetine because they were not marketed in Canada throughout the study period. Attempted and completed suicides were ascertained from hospital and vital statistics databases and then linked to prescription records. Patient follow-up was completed if they switched antidepressants or received augmentation. A propensity score-adjusted analysis* was undertaken to control for confounding by prescribing bias.

**Results:** During the first year of treatment 846 patients attempted or completed suicide (event rate, 6 per 1000 patient years). Most events occurred within the first 6 months of treatment. Risk of completed or attempted suicide did not differ significantly between any antidepressant class and the SSRIs. When individual SSRIs were compared, no clinically important variations in suicide risk were found. Results of analyses restricted to patients without a prior suicide attempt and to those who were treatment-naïve did not differ.

**Discussion:** A major strength of this study is the propensity-score analysis, which allowed the authors to rule out a relationship based on the likelihood that some antidepressants are prescribed more often for patients with greater suicide risk. These findings support the FDA decision regarding the class warning and suggest treatment decisions should be made based on efficacy rather than on suicide risk.

**Editor’s Note:** These authors applied the same research methods to a cohort of pediatric patients and obtained similar results. That article is covered in the current issue of *Child & Adolescent Psychiatry Alerts* and is available at www.alerptubs.com.

Schneeweiss S, Patrick A, Solomon D, Mehta J, et al: Variation in the risk of suicide attempts and completed suicides by antidepressant agents in adults: a propensity score-adjusted analysis of 9 years’ data. *Archives of General Psychiatry* 2010;67 (May):497–506. From Harvard Medical School, Boston, Mass; and other institutions. **Funded by the NIMH.**

The authors disclosed no potential conflicts of interest.

**Drug Trade Names:** bupropion—Wellbutrin, Zyban; duloxetine—Cymbalta; escitalopram—Lexapro

*See Reference Guide.

### Iloperidone Efficacy

One of the newest atypical antipsychotics, iloperidone (*Fanapt*) was approved for acute schizophrenia in May 2009. Four double-blind controlled trials in acute schizophrenia and 1 longer-term maintenance study have been conducted in adult patients. Tolerability data has also been presented. All of the clinical trials were published in industry-sponsored journal supplements.* Clinical trials were reviewed to determine safety and efficacy.

In 3 studies, nearly 1100 patients received acute treatment with 4–24 mg/day iloperidone for 6 weeks. The other controlled trial included 295 patients who received 4 weeks of acute iloperidone titrated to 24 mg/day. Active comparators were haloperidol, risperidone, and ziprasidone. All iloperidone dosages were associated with significant improvements in Brief Psychiatric Rating Scale (BPRS) scores, and 12 and 24 mg/day significantly improved Positive and Negative Syndrome Scale (PANSS) scores. Improvements were comparable to risperidone
and ziprasidone. Long-term efficacy was investigated in 371 iloperidone-treated patients who participated in a 52-week double-blind acute and maintenance trial. In this study, time to relapse (90 days) was not significantly different than with the active comparator haloperidol (102 days).

Adverse effects occurred in 76–81% of iloperidone-treated patients across the studies. The most common were dizziness (14%), dry mouth (5%), and somnolence (5%). It was associated with fewer extrapyramidal symptoms than haloperidol. Weight gain occurred with all dosages, and gains of ≥7% from baseline occurred in 11–15% of treated patients. Most weight gain occurred in the first 6 weeks of treatment. Pooled data showed all iloperidone groups experienced QTc prolongation, but no associated arrhythmias or deaths occurred. Orthostasis and sustained hypertension were also reported and were more frequent with dosages of ≥10 mg/day.

Iloperidone is available in 7 strengths, ranging from 1 to 12 mg per tablet. The recommended starting dose is 1 mg b.i.d. increased in 1–2 mg increments to a target of 6–12 mg b.i.d. within 1 week. No intravenous, intramuscular, or liquid formulations are marketed, but a depot formulation is in development. It should be noted that while iloperidone can be taken with or without meals, food can slow its absorption. Although structurally similar to risperidone, iloperidone is metabolized via cytochrome P450 3A4 and 2D6 and the potential exists for interaction with drugs that inhibit these enzymes (e.g., ketoconazole, fluoxetine). When they must be used together, halving the iloperidone dose is recommended.

Marino J, Caballero J: Iloperidone for the treatment of schizophrenia. *Annals of Pharmacotherapy* 2010;44 (May):863–870. From Nova Southeastern University, Fort Lauderdale, Fla. The authors reported no conflicts of interest.

**Drug Trade Names:** fluoxetine—Prozac; haloperidol—Haldol; iloperidone—Fanapt; ketoconazole—Extina, Nizoral, and others; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

## Anticonvulsants—Comparative Safety

A 2008 meta-analysis led to FDA warnings about increased risk of suicidality with anticonvulsants. A prospective study adds further evidence that gabapentin, lamotrigine, oxcarbazepine, and tiagabine may increase risk. Events were uncommon, occurring in <1% of patients in any group.

**Methods:** Risk of suicidal acts and violent death was evaluated in a cohort of nearly 300,000 patients identified in a research database who had a new anticonvulsant prescription between July 2001 and December 2006. Patients were aged ≥15 years and indications for treatment varied widely. Event rates were calculated for the 180 days following treatment initiation. Topiramate was chosen as the primary reference agent because it is commonly used for a variety of conditions, although not often as first-line treatment for epilepsy. Suicide attempts were identified through emergency department and other hospital records. Suicide and other violent deaths were identified through the Social Security Administration Master Death Index.

**Results:** A total of 868 suicidal and violent death events occurred within 6 months of anticonvulsant initiation (see table, next page). Reported relative risks* (RRs) and hazard ratios* (HRs) are adjusted for age, gender, diagnosis, comorbid conditions, concomitant medications, and other factors. Risk for each individual outcome was increased with gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate. Increased risk was evident within the first 30 days of treatment for all but valproate. A high-dimensional propensity score matched analysis* confirmed the findings for gabapentin, oxcarbazepine, and tiagabine. In particular, rates of attempted or completed suicide for these agents were 5.6, 10, and 14 per 1000 patient years, respectively. Gabapentin increased risk in both adults and young patients, while the
association with oxcarbazepine and tiagabine was found only in adults. Risk was increased with all 3 agents in patients treated for a mood disorder. A repeated analysis using carbamazepine as the reference drug had similar results.

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Treated Patients</th>
<th>Common Conditions</th>
<th>Suicidal/ Violent Death Events</th>
<th>Adjusted HR</th>
<th>Propensity Score Matched RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>57,853</td>
<td>Migraine</td>
<td>115 (0.2%)</td>
<td>Ref. Group</td>
<td>Ref. Group</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>5497</td>
<td>Mood/anxiety disorder</td>
<td>39 (0.7%)</td>
<td>2.4</td>
<td>1.62</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>8579</td>
<td>Mood/anxiety disorder</td>
<td>79 (0.9%)</td>
<td>2.12</td>
<td>1.53</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>142,865</td>
<td>Neuropathic pain</td>
<td>250 (0.2%)</td>
<td>1.42</td>
<td>1.48</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>22,256</td>
<td>Mood/anxiety disorder</td>
<td>186 (0.8%)</td>
<td>1.86</td>
<td>1.31</td>
</tr>
<tr>
<td>Primidone</td>
<td>3104</td>
<td>Mood/anxiety disorder</td>
<td>5 (0.2%)</td>
<td>1.84</td>
<td>2.02</td>
</tr>
<tr>
<td>Valproate</td>
<td>18,295</td>
<td>Mood/anxiety disorder</td>
<td>118 (0.6%)</td>
<td>1.69</td>
<td>0.64</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3975</td>
<td>Epilepsy/seizure disorder</td>
<td>11 (0.3%)</td>
<td>1.66</td>
<td>0.73</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>9086</td>
<td>Neuropathic pain</td>
<td>12 (0.1%)</td>
<td>1.44</td>
<td>1.18</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>3528</td>
<td>Migraine</td>
<td>8 (0.2%)</td>
<td>1.37</td>
<td>3.42</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>9859</td>
<td>Neuropathic pain</td>
<td>21 (0.2%)</td>
<td>1.19</td>
<td>0.73</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10,531</td>
<td>Epilepsy/seizure disorder</td>
<td>20 (0.2%)</td>
<td>1.19</td>
<td>1.98</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>2130</td>
<td>Epilepsy/seizure disorder</td>
<td>4 (0.2%)</td>
<td>0.96</td>
<td>1.64</td>
</tr>
</tbody>
</table>

Discussion: Because of the limited size of the studies included in the FDA meta-analysis and the small number of events, no definitive conclusions could be drawn about safety of individual agents and clinicians were left without a clear picture of comparative safety. This research presents a clearer picture of comparative safety. Despite use of multiple design and analysis components to reduce bias, residual confounding by treatment indication may remain a factor to consider, as patients taking lamotrigine, oxcarbazepine, and tiagabine were treated for mood disorders more often than those in the reference group.

Patorno E, Bohn R, Wahl P, Avorn J, et al: Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303 (April 14):1401–1409. From Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass.; and HealthCore Inc., Wilmington, Del. Funded by HealthCore; and Harvard School of Public Health. Several study authors were employed by or paid consultants to HealthCore.

Drug Trade Names: carbamazepine—Epitol, Tegretol; gabapentin—Neurontin; lamotrigine—Lamictal; levetiracetam—Keppra; oxcarbazepine—Trileptal; phenobarbital—Solfoton, and others; phenytoin—Dilantin, Phenytek; pregabalin—Lyrica; primidone—Mysoline, and others; tiagabine—Gabitril; topiramate—Topamax; valproate—Depakene, Depakote; zonisamide—Zonegran

*See Reference Guide.

Transdermal Rivastigmine Overdose

Serious, sometimes fatal, adverse effects have occurred with improper use of transdermal rivastigmine (Exelon Patch), indicated for dementia associated with Alzheimer’s or Parkinson’s disease. At least 129 medication errors, 2 with fatal outcomes, have been reported with Exelon Patches, most frequently overdose due to not removing an old patch before applying a new one
or applying more than 1 patch. Patients and caregivers should be reminded of the importance of using only 1 patch at a time. Symptoms of rivastigmine overdose include: nausea; vomiting; diarrhea; hypertension; hallucinations; salivation; sweating; respiratory distress; and convulsions. Bradycardia and syncope are also possible. In the case of overdose, all patches should be removed and the patient should be evaluated by a physician. No additional patches should be applied for 24 hours.


### Pregabalin for Anxiety in Substance Abuse

Pharmacologic treatment of anxiety in patients with substance use disorders can be challenging. SSRIs and SNRIs are commonly used, but many patients do not get adequate relief. Clinicians are often reluctant to prescribe adjunctive benzodiazepines because of their abuse and dependence potential.\(^1\)

Off-label use of the anticonvulsant pregabalin (Lyrica) has been effective in generalized anxiety disorder.\(^2\) At SUNY Upstate Medical University, patients with substance use disorders and comorbid anxiety that is partially responsive to an SSRI or SNRI may receive pregabalin augmentation. The charts of 18 consecutive patients were reviewed to evaluate this use.

Pregabalin was administered in the range of 100–600 mg/day (mean, 247 mg/day) for an average of 29 weeks. Overall, improvement in anxiety, insomnia, or pain was reported by 83% of the patients; 11% were much improved and 56% were moderately improved. Weight gain and sedation each affected >15% of treated patients and edema developed in 6%. Four patients reported experiencing affective dyscontrol, anxiety, and irritability after abruptly stopping pregabalin.

In spite of limitations inherent to retrospective case series, these results suggest pregabalin may be moderately effective at reducing resistant anxiety in patients with substance use disorders. It may be a good choice for these patients because it has a lower abuse potential than the benzodiazepines, but the results must be replicated in a prospective study.


### Medication Side Effects – Patient Self-Report

In nonpsychiatric disorders, reported side effects increased substantially when a checklist evaluation was used, compared with nonspecific questioning. The present study, conducted as part of the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, compared side effects collected by checklist and standard clinical assessment in patients with depression. The patients reported substantially more side effects on the checklist than were noted in their records.

**Methods:** Study subjects (n=300) were consecutive patients from a single outpatients psychiatric clinic who were receiving antidepressant therapy for major depression. The sample comprised 89 males and 211 females with a mean age of 45 years; 67% were taking ≥2 psychotropic medications. At the end of a routine appointment patients were given an envelope and asked
by their psychiatrist (who was blinded to the purpose of the study) to complete the enclosed questionnaire. In the envelope was a version of the Toronto Side Effects Scale (TSES) adapted for self-administration. The TSES records the presence and severity of 31 medication side effects. Charts of patients who completed the TSES were then searched to ascertain the side effects recorded during the clinical visit.

**Results:** A large majority of patients (90%) reported at least 1 side effect on the TSES. Most patients (64%) reported experiencing them frequently or every day, but they were usually rated as low severity (≤2 on a 5-point scale). The total number of side effects reported on the TSES was 2301, compared with 167 listed in the progress notes. The mean number of side effects per patient was significantly higher with the TSES (7 vs 1; p<0.01). All 31 TSES items except those related to sexual function were reported significantly more often by patients than by the clinicians. At least 1 side effect was recorded significantly more often in the progress notes for patients who had recently started a new medication, compared with those who had not (39% vs 23%; p<0.01). However, these rates remained substantially lower than TSES rates. When the analysis was limited to side effects that occurred frequently or were very bothersome, the rate of TSES reported occurrences was still 2–3 times higher than in progress notes.

**Discussion:** Side effects are usually evaluated via open-ended questions without reference to specific items. An exception appears to be sexual side effects, which clinicians often inquire about because patients may be embarrassed to disclose them without prompting.

The authors recognize several potential alternative explanations for their findings. Psychiatrists may not systematically record ongoing side effects that had been previously noted. Patients may not spontaneously mention effects to which they have become accustomed, but may endorse them when asked specifically. There is some overlap between the TSES items and symptoms of clinical depression. Physicians may consider some TSES items (e.g., sleep and appetite disturbance, fatigue) as symptoms rather than side effects. However, the authors judge that large and consistent differences between reporting methods do not support these alternative explanations. The authors believe the use of self-administered side effect checklists will improve detection, but it is unclear if and how this will affect medication compliance. They caution that the checklist may heighten patients’ awareness of and anxiety about side effects and that it might not be prudent to use them for patients prone to somatic symptoms.

Zimmerman M, Galione J, Attiullah N, Friedman M, et al: Underrecognition of clinically significant side effects in depressed outpatients. *Journal of Clinical Psychiatry* 2010;71 (April):484–490. From Brown Medical School; and Rhode Island Hospital, Providence. The MIDAS project was funded by the NIH. The authors have no commercial relationships relevant to the article.

**Illicit Buprenorphine Use**

Sublingual buprenorphine is an effective treatment for opioid dependence but is limited by its potential for abuse. Outpatient opioid dependence treatment in the U.S. typically consists of a combination therapy that adds naloxone to block the euphoric high that results from injecting buprenorphine. A survey of opioid-dependent patients found that while illicit buprenorphine use is common, it is rarely intended as a means to produce a high.

Seventy-eight patients from a single community addiction treatment center completed questionnaires about illicit use of buprenorphine in the previous 3 months. A total of 38 patients (49%) reported illicit use. Commonly cited reasons for illicit use were: to prevent cravings (97%) or withdrawal symptoms (90%); relief from pain (47%) anxiety (42%), or depression (40%); and cost savings (29%). Patients who used illicit buprenorphine despite receiving a legally obtained prescription often did so because they felt they needed higher dosages than they were being
prescribed. Few patients (3 of 38; 8%) reported using illicit buprenorphine to get high and none reporting injecting the agent. Follow-up of patients who completed the questionnaires showed illicit use declined by 70% over 3 months of office-based outpatient treatment.

Schuman-Olivier Z, Albanese M, Nelson S, Roland L, et al: Self-treatment: illicit buprenorphine use by opioid-dependent treatment seekers. Journal of Substance Abuse Treatment. Published online April 30, 2010; doi 0.1016/j.jsat.2010.03.014. From Harvard Medical School, Boston, Mass. The study was conducted with no external funding. The authors did not disclose potential conflicts of interest.

Drug Trade Names: buprenorphine—Subutex; buprenorphine–naloxone—Suboxone

Ocular Effects of Psychotropics

The eye appears to be the most common organ to manifest drug toxicity following the liver. A literature review found conventional antipsychotics, TCAs, lithium, topiramate, benzodiazepines, and carbamazepine induce most of the recognized adverse ocular effects of psychotropic medications. However, all psychotropics have the potential to induce ocular effects, most of which can be prevented or successfully treated with awareness and proper treatment.

Angle-Closure Glaucoma is associated with increased intraocular pressure, and if not promptly treated can lead to permanent vision loss. More than 100 cases of angle-closure glaucoma have been reported with topiramate. In addition, TCAs and all of the SSRIs except sertraline have reportedly induced angle-closure glaucoma, probably via their anticholinergic or serotonergic activity. Paroxetine in particular has been implicated in the reaction. Factors associated with increased risk include Hispanic and Asian descent; narrow angle of the anterior ocular chamber; hyperopia; previous occurrence or family history of angle closure; increasing age; female gender; and use of substances that induce papillary dilatation. Ophthalmological examinations are essential for patients with these risk factors before and during TCA therapy. In theory, benzodiazepines and high-dose phenothiazines could also induce angle-closure, but there are no reports with antipsychotic medications and 1 associated with a benzodiazepine.

Eyelid and Corneal Disorders occur most frequently with lithium and phenothiazines. Lithium can increase the sodium content in tears and produce eye irritation. This usually occurs early in treatment and can be managed using artificial tears. High-dose chlorpromazine can cause abnormal eyelid and corneal pigmentation and epithelial keratopathy. Rare but more serious corneal edema, which can be irreversible if not treated promptly, can also occur.

Uveal Tract Disorders including mydriasis (i.e., excessive pupil dilation) and cycloplegia (i.e., paralysis of the ciliary muscle) can result from antagonism of muscarinic receptors. These effects are commonly caused by TCAs and some conventional antipsychotics, probably because of their anticholinergic action, and they produce nonsevere and transient visual disturbances. Topiramate produces ciliary swelling that results in abnormal vision and acute myopia in a small percentage of treated patients. This reaction generally resolves after topiramate is stopped. Visual abnormalities secondary to mydriasis and increased intraocular pressure are being increasingly reported with SSRIs, but they are generally not considered dangerous.

Accommodation Interference underlies blurred vision, which is a common adverse effect of TCAs and phenothiazines. Blurred vision usually resolves without intervention, but prilocaine can be useful when symptoms persist.

Cataract/Pigmentary Deposits can impair passage of light through the ocular lens and reduce vision. Most phenothiazines have been associated with development of eye opacities, but chlorpromazine and thioridazine may present the greatest risk. Haloperidol has not been asso-
associated with cataract, and whether atypical antipsychotics cause the reaction is debated. However, the diabetogenic properties of atypicals could increase risk for cataract and ocular hyperglycemia.

**Retinopathy** refers to non-inflammatory damage to the retina and is usually associated with systemic disease. Thioridazine and chlorpromazine have been linked to pigmentary retinopathy, which can lead to vision loss. High doses are considered hazardous to the retina.

**Other Disorders** such as oculogyric dystonia have been reported with atypical antipsychotics, particularly risperidone; with carbamazepine and topiramate; and rarely with SSRIs. Lithium, carbamazepine, and topiramate can induce nystagmus. Carbamazepine can lead to decreased color and contrast perception. TCAs can cause decreased tear formation, and trazodone has induced palinopsia (i.e., persistent images of recently viewed objects).

Richa S, Yazbek J-C: Ocular adverse effects of common psychotropic agents: a review. CNS Drugs 2010;24(6):501–526. From Psychiatric Hospital of the Cross, Beirut, Lebanon. The study was conducted with no external funding. The authors have no conflicts of interest relevant to this material.

**Drug Trade Names**: carbamazepine—Epitol, Tegretol; chlorpromazine—Thorazine; haloperidol—Haldol; paroxetine—Paxil; risperidone—Risperdal; sertraline—Zoloft; thioridazine—Mellaril; topiramate—Topamax; trazodone—Desyrel, and others

**Reference Guide**

**Journal Supplements**: Biomedical journals sometimes publish supplements devoted to specific topics. These may be financed by for-profit organizations or by organizations representing for-profit interests and may be produced outside of the routine editorial and peer review processes of the journal. Some publishers require that journal supplements meet the same rigorous standards as the parent journal; others do not. Despite their inherent limitations, according to a recent editorial in the *Lancet*, journal supplements can be made to work, although research suggests that the quality of supplement material is usually much inferior to that of any parent title [Lancet 2010;375 (January 30):347].

**Hazard Ratio**: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Propensity Score Matching**: Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is a correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

**Relative Risk**: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.