Pseudoephedrine for Clozapine Incontinence

A 58-year-old man with psychosis had been unsuccessfully treated with multiple trials of conventional and atypical antipsychotics, antidepressants, mood stabilizers, and anxiolytics.\(^1\) His psychiatric status remained unstable, and he was hospitalized and started on clozapine (Clozaril). Results of laboratory analyses (e.g., white blood cells, absolute neutrophil counts) remained within normal limits after clozapine initiation, and his psychotic symptoms improved. However, soon after starting clozapine, the patient became incontinent. Because ephedrine had previously been associated with resolution of clozapine-induced incontinence, the patient was started on 30 mg pseudoephedrine 4 times per day. Within 3 days, the incontinence resolved and did not recur over >1 month of inpatient follow-up.

Clozapine is often reserved as a last resort treatment because of its potential to cause blood dyscrasias. According to the package label for Clozaril, urinary incontinence affects <1% of clozapine-treated patients.\(^2\) However, it has been estimated that as many as 42% of patients taking an atypical antipsychotic experience enuresis. The mechanism by which clozapine induces incontinence is unclear, but it is possible that the potent antiadrenergic activity could reduce bladder tone of the internal sphincter. Overflow incontinence is also possible as a result of urinary retention induced by clozapine’s muscarinic receptor antagonism. Clozapine-induced incontinence can be treated with dosage reduction or by switching to an agent with less anticholinergic activity; usual incontinence medications can be intolerable and are often ineffective. For many patients, clozapine is the only treatment that effectively manages their schizophrenia symptoms, and incontinence may cause them to discontinue therapy. A trial of pseudoephedrine may allow these patients to continue receiving clozapine.


**Schizophrenia "Meta-Guidelines"**

A meta-guideline—or "guideline of guidelines"—for the management of schizophrenia has been compiled by researchers at the University of California–San Diego and other institutions. The goal of this project was to present a comprehensive, clinically useful guideline that reconciles contradictions among existing guidelines and that includes information on novel therapeutic agents. The meta-guideline was based on existing recommendations, updated with current information, and synthesized from recommendations published in the past 10 years. Sources included the Agency for Healthcare Research and Quality’s Patient Outcomes Research Team (PORT), the Texas Medication Algorithm Project, and the American Psychiatric Association, as well as various state and federal hospitals and expert opinion authors. The meta-guideline was extensively reviewed by multiple peer reviewers.

*Editor’s Note:* The original article contains a series of valuable, easy-to-read tables that make up these meta-guidelines. The editors at M.J. Powers & Co. Publishers recommend that our readers view the original article, available as a free view-only PDF at http://journals.cambridge.org.

Stahl S, Morissette D, Citrome L, Saklad S, et al: "Meta-guidelines" for the management of patients with schizophrenia. *CNS Spectrums* 2013; doi 10.1017/S109285291300014X. From The University of California–San Diego; and other institutions. Source of funding not stated. Four of the study authors disclosed relationships with commercial sources; the remaining 5 declared no conflicts of interest.

**Depression, Antidepressants, and *C. difficile* Infection**

Both depression and treatment with certain antidepressant drugs were associated with increased risk of *Clostridium difficile* infection in a pair of epidemiologic studies.

*Methods:* Investigators analyzed data from the nationally representative, longitudinal, Health and Retirement Study (HRS) of older Americans, using study interviews conducted in 1992–2006 and linked to Medicare data. Both major depression and *C. difficile* infection were identified based on physician diagnosis. The analysis also included a wider group of patients with "depressive disorders," such as brief or prolonged depressive reactions; adjustment reactions; depressive psychosis; bipolar disorder; and neurotic depression.

To explore the association of specific antidepressants with *C. difficile* infection, a hospital-based case-control study was also conducted in patients aged ≥18 years, admitted to a single institution over 19-months. All study participants were admitted for reasons other than *C. difficile* infection but had stool tests 48 hours or more after admission, presumably because they were symptomatic.

*Results:* The HRS sample consisted of 16,781 participants with a mean age of 68 years. After adjusting for multiple risk factors, patients with major depression had a significant increase in the odds for *C. difficile* infection (odds ratio,* 1.36; p=0.016). Risk was increased by a similar proportion in patients who had the broader range of depressive disorders. Higher risk of infection was also associated with widowhood and with living alone.

Of the 4047 patients in the case-control study, 468 had stool samples that tested positive for *C. difficile* and were considered case patients. Case and control patients were similar, both clinically and demographically. However, use of certain antidepressants was more common in cases; both mirtazapine and fluoxetine were associated with significantly increased odds of *C. difficile* infection (mirtazapine adjusted odds ratio, 2.14; p=0.003; fluoxetine adjusted odds ratio, 1.92; p=0.012). The relationship was dose-related for both drugs. Nortriptyline was associated with dose-related risk of infection, but the odds ratio for use versus non-use was not statistically significant. No other individual antidepressants were associated with *C. difficile* infection. The combination of mirtazapine with trazodone was linked with even higher risk (odds ratio, 5.72 compared with users of neither of these drugs; p=0.001).
Discussion: The investigators could not determine whether depression or antidepressant drugs was the main driver of these associations. Other research has suggested that depression may be associated with immune dysregulation and altered gut microbiota. There is some evidence from longitudinal studies that depression and bowel disease may be expressions of a partly shared etiologic process that might begin early in life. *C. difficile* is the most common cause of antibiotic-associated diarrhea. Clinicians who prescribe antibiotics to patients with depression, especially those receiving fluoxetine or mirtazapine, should be aware that they may already be at increased risk of infection.

Rogers M, Greene M, Young V, Saint S, et al: Depression, antidepressant medications, and risk of *Clostridium difficile* infection. *BMJ Medicine* 2013;11:121. From the University of Michigan and the Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI. Funded by the National Institute of Allergy and Infectious Diseases. The authors declared no conflicts of interest.

Drug Trade Names: fluoxetine—Prozac; mirtazapine—Remeron; nortriptyline—Aventyl, Pamelo; trazodone—Desyrel

*C*See Reference Guide.

### Citalopram Warning Questioned

In a large cohort of patients with depression, risk of ventricular arrhythmia and mortality were not increased in patients receiving higher-than-recommended doses of citalopram. This result calls into question the continued merit of the FDA’s warning to avoid citalopram dosages exceeding 40 mg/day.

**Background:** The 2011 and 2012 FDA warnings concerned the potential for dose-dependent QT interval prolongation and torsades de pointes and indicated that citalopram dosages >40 mg/day (or >20 mg/day in patients aged >60 years or with certain risk factors) should no longer be prescribed. The FDA decision was based on postmarketing reports of QT prolongation and the results of a single unpublished, placebo-controlled, crossover study in 119 patients. Risks of negative patient-centered health outcomes, such as ventricular arrhythmia and cardiac mortality, have not been previously evaluated.

**Methods:** Data was analyzed from a Veterans Health Administration (VHA) registry of all patients receiving treatment for depression. Included in the analysis were >618,000 VHA patients given a prescription for citalopram between 2004 (the year in which it was introduced as a generic) and 2009 and a comparison group of nearly 366,000 patients given a prescription for sertraline, which has no FDA warning. Study outcomes, ascertained after the first prescription of each drug, were ventricular arrhythmias, mortality from cardiac and noncardiac causes, and total mortality. The analysis was adjusted for a large number of factors that might influence risk of the study outcomes.

**Results:** Patients had a mean age of 57 years, and 90% were men. High-dose treatment (i.e., >40 mg/day citalopram or >100 mg/day sertraline) was prescribed for 19% and 36% of the citalopram and sertraline groups, respectively. Slightly more than one-third of the sample received concomitant medication noted to potentially cause torsades des pointes; the rate did not differ between groups.

Ventricular arrhythmia occurred in 1.1% of the citalopram cohort and 1.1% of the sertraline cohort. A total of 3.3% and 4.0% of patients in the citalopram and sertraline cohorts, respectively, died from cardiac causes. Rates of each adverse outcome decreased with higher doses of each antidepressant. In the adjusted analysis, citalopram dosages >40 mg/day were associated with significantly lower risk of ventricular arrhythmia compared with dosages of ≤20 mg/day (hazard ratio,* 0.68). The highest doses were also associated with significantly lower all-cause mortality (hazard ratio, 0.94) and noncardiac mortality (hazard ratio, 0.90).
Risks were intermediate in patients receiving doses between 20 and 40 mg. For most outcomes, a similar pattern occurred in patients who received sertraline.

**Discussion:** The present analysis calls the FDA’s warning into question, and the authors suggest it may do more harm than good. Citalopram has been used safely by many patients over a long period of time, is available as an inexpensive generic, and is an antidepressant of choice on many formularies. Several existing national and international studies and a meta-analysis have shown benign outcomes associated with citalopram use.


**Drug Trade Names:**
- citalopram—Celexa
- sertraline—Zoloft

*See Reference Guide.

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**Bupropion for Binge Eating Disorder**

In a placebo-controlled trial, bupropion produced significant but modest reductions in body mass index (BMI) in a group of overweight women with binge eating disorder. Relative to placebo, however, the agent did not improve patients’ binge eating, food craving, or depression.

**Background:** In addition to reducing binge eating, weight reduction is an important aim of treatment of binge eating disorder. Several medications, notably SSRIs and orlistat, have shown mixed or statistically significant but modest effects on weight in this disorder. The anticonvulsants topiramate and zonisamide are more effective but associated with high rates of adverse effects and discontinuation. Cognitive behavioral therapy is effective in reducing binge eating but does not reduce weight.

**Methods:** Subjects in this controlled trial were 61 overweight or obese (BMI, ≥25) women who met DSM-IV-TR research criteria for binge eating disorder. Participants had a mean age of 44 years and a mean BMI of 36. A total of 32 women (16 in each group) had a comorbid mood disorder. The women were randomly assigned to 8 weeks of double-blind treatment with either 150 mg b.i.d. sustained-release bupropion or placebo. Outcomes assessed bi-weekly included weight, the Eating Disorder Examination, the Food-Craving Inventory, and the Beck Depression Inventory. Assessments also included daily self-monitoring and recording of bulimic episodes. Remission was defined as 28 days of continuous abstinence from binge eating.

**Results:** All clinical outcomes—BMI, eating psychopathology, food craving, binge eating episodes, and depressed mood—improved over the course of the study in both treatment groups. Patients who received bupropion had significantly greater mean reductions in BMI than those who received placebo, but the absolute change was small: 0.5 versus 0.2 points (p=0.002), respectively. Average weight loss was 3.7 lbs with bupropion and <1 lb with placebo. No other outcome variable differed between the bupropion and placebo groups. By study end, 42% of the bupropion group and 27% of the placebo group had achieved remission (p=ns).

**Discussion:** The magnitude of the effects of bupropion in the present study is similar to those of other pharmacotherapy-only trials. They indicate that 300 mg/day bupropion has no role as stand-alone therapy for the disorder. Future studies should investigate bupropion at higher doses, in longer trials, and in combination with CBT or behavioral programs.

White M, Grilo C: Bupropion for overweight women with binge-eating disorder: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Psychiatry 2013;74 (April):400–406. From Yale University, New Haven, CT. **Funded by the NIH. The authors declared no conflicts of interest.**

**Drug Trade Names:**
- bupropion—Wellbutrin
- orlistat—Xenical
- topiramate—Topamax
- zonisamide—Zonegran
ACE Inhibitor Hallucinations in Elderly

Use of antihypertensives, including angiotensin-converting enzyme inhibitors, is increasing in the rapidly aging Western population. Common adverse effects of ACE inhibitors include cough; rash; angioedema; hypotension; hyperkalemia; and renal insufficiency. Although not listed in product labels, ACE inhibitor-related visual hallucinations have also been reported, primarily in elderly patients.

Researchers from the University of Utah report 4 cases of lisinopril-associated hallucinations in patients aged 92–101 years (3 women). All 4 patients had some degree of cognitive impairment. Hallucinations developed within several months of starting lisinopril in 2 patients and after 1 and 7 years of therapy in the other 2 patients. The hallucinations resolved in all 4 patients with lisinopril discontinuation. One patient underwent rechallenge; hallucinations recurred and again resolved with lisinopril discontinuation.

A literature search for other reports of ACE inhibitor-associated hallucinations identified 7 additional published reports and 14 unpublished reports that had been made to the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA). These reports were associated with use of cilazapril (n=1); captopril (n=6); enalapril (n=3); lisinopril (n=4); perindopril (n=1); quinapril (n=2); and ramipril (n=3) monotherapy; 1 patient received both captopril and enalapril.

In the 25 total cases, the majority of patients (n=18; 72%) were aged ≥65 years (range, 17–101 years), and gender distribution was nearly equal. After ACE inhibitor discontinuation, hallucinations were reduced in 1 patient and resolved in 21 patients (84%), most within 10 days. Three patients’ hallucinations did not resolve, and 1 patient continued medication despite the hallucinations.

Although the association between the ACE inhibitor and visual hallucinations was not proven to be causal in these patients, the resolution with medication discontinuation and prompt recurrence with rechallenge suggest this is the case. Advancing age and possible underlying central nervous system disorders may be risk factors for ACE inhibitor-associated hallucinations. As the elderly population grows, recognition of adverse CNS effects becomes more important, as does knowledge of the potential for associated hallucinations.


Drug Trade Names: captopril—Capoten; cilazapril (not available in U.S.)—Inhibace; enalapril—Vasotec; lisinopril—Prinivil, Zestril; perindopril—Aceon, Coversyl; quinapril—Accupril; ramipril—Altace, Tritace

Discontinuing or Switching Antidepressants: Guidelines

To summarize all available knowledge on switching or discontinuing antidepressants, investigators reviewed tertiary compilations of drug information, antidepressant package inserts, and electronic publication databases. The authors found that the few existing guidelines that aim to be comprehensive still contain many gaps and are based in part on non-primary sources such as package inserts and references on file with pharmaceutical companies. There have been few, if any, trials designed specifically to evaluate the utility or efficacy of specific approaches to switching or discontinuing antidepressants.

In withdrawing antidepressants, the primary goal is to avoid discontinuation symptoms. These symptoms are most common: after ≥5–8 weeks of treatment; in patients taking higher doses of the drug; in those with compliance problems; and with drugs with a shorter half-life or with nonlinear pharmacokinetics (e.g., paroxetine). Drugs with a shorter half-life require a longer taper, possibly as long as 6–12 months. A 25% dose reduction per week is generally
recommended to prevent discontinuation syndrome, but a recent article recommends a more gradual taper for all antidepressants: a 25% dose decrease per month, or 12.5% every 2 weeks. Studies have not determined which method is best. See table for suggested length of taper.

Factors to consider when switching antidepressants include safety; potential drug interactions; pharmacokinetic properties of the drugs; cost; and patient preference. Patients who are being switched because of a lack of response should be closely monitored for worsening depression and suicidal ideation during the switch. Cross-tapering is the best approach for most patients, even if the 2 drugs are members of the same class. Cross-tapering maintains the antidepressant effect while reducing the potential for drug interactions. A direct switch can be used if the first antidepressant has been taken for \( \leq 1 \) week. Tapering, with or without a washout, should be considered if there is a significant potential for drug interaction. A washout of 5 times the half-life is needed when switching to or from an MAOI.

Ogle N, Akkerman S: Guidance for the discontinuation or switching of antidepressant therapies in adults. *Journal of Pharmacy Practice* 2013; doi 10.1177/0897190012467210. From the University of Kansas Hospital, Kansas City; and the Nebraska Medical Center, Omaha. *This research was conducted without funding. The authors declared no conflicts of interest.*

**Drug Trade Names:**
- Bupropion—Wellbutrin
- Citalopram—Celexa
- Clomipramine—Anafranil
- Duloxetine—Cymbalta
- Escitalopram—Lexapro
- Fluoxetine—Prozac
- Fluvoxamine—Luvox
- Mirtazapine—Remeron
- Nefazodone—Serzone
- Paroxetine—Paxil
- Phenelzine—Nardil
- Sertraline—Zoloft
- Tranylcypromine—Parnate
- Trazodone—Desyrel
- Venlafaxine—Effexor
- Vilazodone—Viibryd

### Terazosin for Antidepressant-Associated Sweating

Results of a pilot study suggest that terazosin may be a safe and effective treatment for excessive sweating associated with antidepressants.

**Background:** Excessive sweating (i.e., hyperhidrosis) affects 5–14% of patients taking an antidepressant and persists throughout treatment. It has been reported with TCAs, SSRIs, SNRIs, and bupropion. Hyperhidrosis is believed to be caused by central serotonergic dysfunction. Although case reports suggest that some antiserotonergic, antiadrenergic, and anticholinergic medications may be effective, there is no clinical trial data available on treatment of antidepressant-associated hyperhidrosis.

**Methods:** Researchers conducted 2 uncontrolled, open-label pilot studies (1 unfunded) examining terazosin in a total of 23 patients, aged 18–75 years, with major depression and a \( \geq 1 \)-month history of antidepressant-associated hyperhidrosis of at least moderate severity. Patients had a median age of 48 years, 78% were women, and two-thirds had experienced excessive sweating with a previous antidepressant. Current antidepressants included: venlafaxine (n=5); duloxetine (n=3); escitalopram (n=3); sertraline (n=3); bupropion (n=2); citalopram (n=2); fluoxetine (n=2); clomipramine (n=1); sertraline plus bupropion (n=1); and venlafaxine plus bupropion (n=1). Following a 2-week baseline period, during which sweating was assessed by self-report and clinical measures, participants received 6 weeks of terazosin treatment. The starting dosage was 1 mg/day and could be increased by 1 mg/week to a maximum of 6 mg/day. Patients performed self-assessments daily and were assessed at the clinic weekly. Outcomes included changes in sweating and quality of life.
Results: Because the 2 studies were small and nearly identical, the patient populations were pooled and the results were presented together. Patients reported that excessive sweating was most prominent in the face (95%), scalp (62%), neck (48%), and chest (57%); few patients reported it affecting their armpits or palms. At baseline, patients had reported distressing effects of hyperhidrosis including: making them "extremely" or "very" uncomfortable (96%), embarrassment (83%), and causing them to stay at home (48%). At 6 weeks, 22 of the 23 patients (97%) met response criteria (Clinical Global Impression-Improvement* score 1 or 2). Following terazosin treatment, patient-rated severity of sweating and proportion of time affected by the sweating significantly decreased (p=0.004 and p<0.001, respectively). Although general quality of life was not significantly improved, the intrusiveness of hyperhidrosis was significantly reduced.

Nearly 70% of patients reported ≥1 adverse effect; the most common were dizziness/light-headedness (n=10), dry mouth (n=5), and nausea (n=3). These resolved in most patients, and no patient withdrew from the study because of adverse effects. Three patients experienced an orthostatic change in systolic blood pressure (a decrease of ≥10 mm Hg).

Discussion: Excessive sweating can lead to medication nonadherence. Although dosage reduction or switching medication are recommended as first-line treatment, these strategies are not viable for all patients. Results of these pilot studies, while preliminary, suggest that terazosin may be an effective treatment for antidepressant-associated hyperhidrosis. However, because dizziness/light-headedness and orthostatic hypotension can occur, caution is warranted when using terazosin in the elderly and in patients receiving an antihypertensive or other medication that can cause orthostatic hypotension.

Mago R, Thase M, Rovner B: Antidepressant-induced excessive sweating: clinical features and treatment with terazosin. Annals of Clinical Psychiatry 2013;25 (May):E1–E7. From Jefferson Medical College, Philadelphia, PA. One study was conducted with no external funding; the other was funded by NARSAD; and other institutions. The study authors disclosed financial relationships with commercial sources.

Drug Trade Names: bupropion—Wellbutrin; citalopram—Celexa; clomipramine—Anafranil; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; sertraline—Zoloft; terazosin—Hytrin; venlafaxine—Effexor

*See Reference Guide.

Varenicline for Alcohol Dependence

In a multi-site, phase 2 controlled trial, the nicotinic acetylcholine agonist varenicline reduced alcohol consumption and craving in a group of patients with alcohol-dependence.

Methods: Study subjects were 200 adults (142 men) with DSM-IV-TR alcohol dependence who had responded to study advertisements at 5 academic sites in the U.S. Female participants were required to consume an average of ≥28 standard drinks per week, and male participants an average of ≥35 drinks per week. After screening and baseline visits, participants were stratified by smoking status, and then randomized to 13 weeks of double-blind treatment with either varenicline or placebo. The target varenicline dosage was 1 mg b.i.d. All patients also participated in a 6-session self-help bibliotherapy program designed to reduce drinking. The primary outcome was number of heavy drinking days, defined as having consumed ≥4 and ≥5 drinks in a day for women and men, respectively. Secondary outcomes included: drinks per day; drinks per drinking day; percentage of days abstinent; alcohol craving; alcohol-related consequences; and quality of life.

Results: At baseline, there were no significant differences between the placebo and varenicline groups in any characteristics. Study participants consumed an average of 13 drinks per day and met criteria for a heavy drinking day about 88% of days. For the majority of participants (56%), the desired outcome was controlled drinking; 28% desired permanent abstinence. A total of 78 patients (39%) were self-reported smokers.
During treatment, patients taking varenicline averaged significantly fewer heavy drinking days per week than those who received placebo: 38% of days vs. 48% of days (p=0.03; effect size,* 0.31). Treatment effects were not altered by baseline smoking status. Compared with the placebo group, the varenicline group also reported: consuming significantly fewer drinks per day (4.4 vs. 5.3; p=0.03; effect size, 0.29); fewer drinks per drinking day (5.8 vs. 6.8; p=0.03; effect size, 0.26); and a lower percentage of very heavy drinking days (18 vs. 26; p=0.047; effect size, 0.25). In addition, alcohol craving scores were significantly lower in patients who received varenicline (10 vs. 12; p=0.01; effect size, 0.33). Neither the percentage of abstinent patients (2%) nor the percentage of days abstinent (36–40%) differed between groups. There were also no significant between-group differences in quality of life or alcohol-related consequences.

Varenicline was generally well tolerated. Nausea, abnormal dreams, and constipation occurred significantly more often in the varenicline group, but most cases were mild. There were no significant differences between groups on mood and behavioral/thinking assessments, and varenicline did not increase suicidal ideation, hostility, or agitation.

**Discussion:** There are currently 3 agents FDA approved for treatment of alcohol dependence: disulfiram, naltrexone, and acamprosate. Varenicline is currently FDA approved for smoking cessation. The effect sizes produced by varenicline in the present study are comparable to those reported in naltrexone and acamprosate trials, suggesting varenicline may be another viable option for treatment of alcohol dependence.

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

Litten R, Ryan M, Fertig J, Falk D, et al: A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *Journal of Addiction Medicine* 2013; doi 10.1097/ADM.0b013e31829623f4. From the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, MD. **Funded by the NIAAA. The authors declared no conflicts of interest.**

**Drug Trade Names:** acamprosate—Campral; disulfiram—Antabuse; naltrexone—Depade, ReVia, Vivitrol; varenicline—Chantix

*See Reference Guide.

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**Reference Guide**

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

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

**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.

**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.