

# Letters to the Editor

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## CLONIDINE AND AUDITORY HALLUCINATIONS

Dear Editor:

Clonidine is used to manage a variety of psychiatric symptoms in addition to general medical conditions such as hypertension and pain. We report a case of auditory hallucinations in the context of clonidine use.

**Case report.** A 53-year-old African-American man was in a motor vehicle accident that resulted in multiple orthopedic surgeries and an extensive rehabilitation process. He had no prior psychiatric history. He was referred to psychiatry for management of depression and posttraumatic stress disorder (PTSD). The depressive symptoms responded well to sertraline; however, he continued to have intrusive flashbacks and significant disruption of sleep due to recurrent nightmares about the accident. He would wake up screaming and crying. Clonidine was initiated at 0.05mg and gradually titrated to 0.15mg at night. Thereafter, flashbacks and nightmares disappeared and sleep improved; however, he started hearing a voice that referred to him in third person. Clonidine was discontinued, following which the hallucinations stopped, although nightmares and flashbacks recurred.

**Discussion.** Clonidine is a central presynaptic  $\alpha_2$ -agonist that causes a reduction in sympathetic activity. This decrease in central noradrenergic activity is the likely underlying mechanism for clonidine, causing a reduction in PTSD symptoms such as nightmares and startle reaction.<sup>1</sup> Common adverse effects of clonidine include sedation, dizziness, fatigue, and rebound hypertension with sudden discontinuation. Rarely, anxiety, depressive symptoms, sleep

disturbances, and hallucinations have also been reported.<sup>2</sup> A PubMed literature search using the terms *clonidine* and *hallucinations* revealed only four case reports. One case report included three patients, two of which experienced visual hallucinations.<sup>3</sup> Another case report reported the emergence of auditory hallucinations and paranoia with the use of clonidine for management of severe hypertension.<sup>4</sup> Since clonidine is frequently used for a variety of psychiatric disorders, such as attention deficit hyperactivity disorder, tic disorders, aggression, and opiate withdrawal, it is essential to be aware of and to monitor for this rare but serious adverse effect.

### References

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With regards,

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## NEW UNCONTROLLED BENZODIAZEPINE, PHENAZEPAM, EMERGING DRUG OF ABUSE

Dear Editor:

Phenazepam is a long-acting benzodiazepine that was developed in the former Soviet Union in the 1970s. It is not a scheduled drug here in the United States or in most of Western Europe. Phenazepam has become a drug of concern due to the number of hospitalizations and fatalities following overdoses.<sup>1–3</sup> The drug is potent at one-tenth of the recommended dose for diazepam.<sup>3</sup> The lack of data on this drug highlight the need for healthcare professionals to be aware of its existence.<sup>1</sup>

In Russia, the indications for phenazepam are epilepsy, anxiety, and sleep disorders.<sup>1</sup> Its increase in use for nonmedicinal purposes has been reported in Western Europe in the last couple of years, and its use has spread to the United States, with recorded deaths resulting from its use in Georgia and Louisiana.<sup>1,4,5</sup> Some of phenazepam's concerning side effects include loss of coordination, drowsiness, and amnesia.<sup>5</sup> I believe the latter side effect to be particularly concerning due to its potential for use as a date rape drug.

Fatalities have been reported when the drug is taken with other prescription opioid analgesic drugs.<sup>4</sup> Phenazepam has been referred to as *benzo-relaxation* by its users.<sup>4</sup>

As mentioned previously, phenazepam is not a controlled substance in the United States and in parts of Europe and can be obtained over the internet, where it has been sold either as a tablet or as crystalline powder.<sup>2</sup> In the United States, it has

been sold as an air freshener known as “Zannie.” Reports indicate that spraying Zannie into the mouth is the main route of administration, and when used with antidepressants, sleep medications, pain medications, or alcohol, it can prove fatal.<sup>5</sup> The product Zannie was tested at the Louisiana Poison Center, which revealed that the product contains 100-percent phenazepam.<sup>5</sup> As a result, legislators in Louisiana have filed a bill to make the product illegal in the state.

The detection of phenazepam in the blood stream has been demonstrated using gas chromatography (GC), gas chromatography/mass spectrometry (GC/MS), and liquid chromatography/mass spectrometry (LC/MS), but there are no data regarding the sensitivity of available immunoassays.<sup>3</sup>

The need for healthcare personnel to be aware of phenazepam, its symptoms of use, and its risk of death by overdose alone or by use with other substances cannot be overstated, particularly in emergency room settings.

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### AGGRESSIVE BEHAVIORS AND PAST MENTAL HEALTHCARE UTILIZATION AMONG INTERNAL MEDICINE OUTPATIENTS

Dear Editor:

The association between aggression/violence and mental disorders continues to be controversial. For example, a number of studies have reported associations between violence and mental disorders,<sup>1,2</sup> and violence risk appears to be empirically higher in individuals with psychosis,<sup>3-6</sup> including schizophrenia,<sup>7,8</sup> as well as among those with personality disorders and substance abuse.<sup>7</sup> However, Stuart<sup>9</sup> emphasized that, “...mental disorders are neither necessary, nor sufficient causes of violence.” In this study, using a consecutive sample of internal medicine outpatients, we further

examined the controversial associations between aggression and mental disorders using a unique methodology.

Participants in this study were men and women, ages 18 years or older, who were being seen at an internal medicine outpatient clinic staffed predominantly by resident providers. The recruiter excluded individuals with symptoms of a severity that would preclude the candidate’s ability to successfully complete a survey (n=62, mostly language difficulties).

At the outset, 480 individuals were approached, and 369 agreed to participate (participation rate of 76.9%). Of these, 338 completed the relevant study measures, 230 (68.0%) women, 106 (31.4%) men, and 2 (0.6%) who did not indicate their gender. Participants ranged in age from 18 to 87 years (median [M]=49.99, standard deviation [SD]=15.58), and most were White/Caucasian (86.0%) followed by African-American (9.3%). All but 7.5 percent had at least graduated high school whereas 29.4 percent had earned a four-year college degree or higher.

During clinic hours, one of the authors (JSL) positioned himself in the lobby of the outpatient clinic, approached consecutive incoming patients, and informally assessed exclusion criteria. With potential candidates, the recruiter reviewed the focus of the project and then invited each to participate by completing a six-page survey. Participants were asked to place completed surveys into sealed envelopes and then into a collection box in the lobby.

The survey consisted of three sections, the first being a demographic query. The second section explored participants’ past mental health history: 1) “Have you ever seen by a psychiatrist?” 2) “Have you ever been hospitalized in a psychiatric hospital?”

**APPENDIX: Aggressive Behavior Questionnaire (ABQ)**

As an adult (ages 18 and older), have you ever:

Yes	No		
___	___	1.	Punched a wall when angry?
___	___	2.	Intentionally broken things when angry?
___	___	3.	Hit your partner when angry?
___	___	4.	Hit a child out of anger, not because of discipline?
___	___	5.	Caused and gotten into a bar fight?
___	___	6.	Gotten into fist fights (not in a bar)?
___	___	7.	Mistreated an animal when angry?
___	___	8.	Killed an animal when angry?
___	___	9.	Been charged with assault (not necessarily convicted of it)?
___	___	10.	Damaged anyone else's car on purpose?
___	___	11.	Damaged the property of others to "get back" at them?
___	___	12.	Stolen from anyone because of anger, not need?
___	___	13.	Defaced public property (e.g., walls, buildings, parks)?
___	___	14.	Intentionally ran anyone off the road?
___	___	15.	Beat up anyone such that they required medical attention?
___	___	16.	Pushed or shoved a partner when angry?
___	___	17.	Caused anyone to have an "accident"?
___	___	18.	Bullied a partner into sex?
___	___	19.	Spit at or on anyone?
___	___	20.	Bitten anyone?
___	___	21.	Threatened anyone with a weapon?

**TABLE 1.** Mean scores on the measure of different forms of aggressive behavior (ABQ) as a function of mental healthcare utilization

Have you ever...	No		Yes		F	p <
	M	(SD)	M	(SD)		
seen a psychiatrist?	1.66	2.16	3.87	3.69	47.88	0.001
been hospitalized psychiatrically?	2.3	2.81	4.02	4.01	13.83	0.001
been in counseling?	1.67	2.44	3.4	3.37	28.86	0.001
been on medication for nerves?	1.68	2.25	3.69	3.58	39.59	0.001

Note: *df*=1,336 for F tests

3) "Have you ever been in counseling?" and 4) "Have you ever been on medication for your nerves?" The third section contained an author-developed 21-item questionnaire designed to explore lifetime aggressive behaviors (labeled, "Aggressive Behavior Questionnaire," or ABQ; see appendix). With yes/no response options, the total number of affirmative

responses is considered a general measure of the different forms of aggressive behavior in which the respondent has engaged.

This project was reviewed and exempted by two institutional review boards. Completion of the survey was assumed to function as implied consent and was explained as such for the patients on the cover page.

Of the 338 respondents, 137 (40.5%) had been seen a psychiatrist, 50 (14.8%) had been hospitalized in a psychiatric hospital, 173 (51.2%) had been in counseling, and 149 (44.1%) had been on medication for their nerves. Scores on the ABQ ranged from 0 to 17 (*M*=2.56, *SD*=3.07), with 32.8 percent of respondents denying having engaged in any of the aggressive behaviors.

Scores on the ABQ are presented in Table 1 as a function of whether respondents reported each form of mental healthcare utilization. Across all forms of utilization, respondents who reported mental healthcare utilization had higher scores on the measure of aggressive behavior compared to their peers who did not report mental healthcare utilization.

To investigate the unique predictive power of each in explaining ABQ scores, we performed a multiple regression analysis in which all four forms of mental healthcare utilization were simultaneously entered as predictors of ABQ scores. As expected, the overall equation was statistically significant: *R*=0.40, *F*(4,331)=15.82, *p*<0.001. Importantly, only two forms of mental healthcare utilization were independently predictive of ABQ scores after controlling for the effects of the remaining predictor variables: having seen a psychiatrist (*Beta*=0.24, *t*=3.49, *p*<0.001) and having ever been on medications for nerves (*Beta*=0.20, *t*=3.27, *p*<0.001). Both having been in counseling (*Beta*=0.03, *t*=0.44, *p*<0.67) and having been hospitalized in a psychiatric hospital (*Beta*=0.01, *t*=0.17, *p*<0.88) were not uniquely related to scores on the ABQ.

In this study, univariate analyses indicated that all mental-healthcare-utilization variables were significantly related to scores on the measure of lifetime aggressive behaviors. In multivariate analyses, only two variables remained uniquely predictive:

being seen by a psychiatrist and having been on medications for “nerves.” While we did not examine psychiatric comorbidity, various factors may moderate these findings, such as substance abuse and/or personality pathology, both of which have previously been associated with violence and aggression.

This study has a number of potential limitations. First, all data are self-report in nature. Second, we did not undertake any assessment of psychiatric diagnoses; therefore, we do not know the mediating and moderating roles of specific forms of mental disorders. Third, the ABQ is an unvalidated measure of aggression. Fourth, we cannot infer a causal relationship between mental disorder and violence based upon the current methodology (i.e., a cross-sectional approach). Despite these potential limitations, the sample size is reasonable, the study population of consecutive primary care patients is atypical in this area of study, and the use of the ABQ is a novel measure. Findings underscore relationships between aggression and past mental healthcare utilization.

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