Lead Poisoning; a Neglected Potential Diagnosis in Abdominal Pain

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Mahtab Shabani
Shahid Beheshti University of Medical Sciences School of Medicine

Seyed Kaveh Hadeiy
Shahid Beheshti University of Medical Sciences School of Medicine

Parinaz Parhizgar
Shahid Beheshti University of Medical Sciences School of Medicine

Nasim Zamani
Shahid Beheshti University of Medical Sciences School of Medicine

Hamid Mehrad
Shahid Beheshti University of Medical Sciences School of Medicine

Hossein Hassanian-Moghaddam
Shahid Beheshti University of Medical Sciences School of Medicine

✉ hassanian@sbmu.ac.ir
Corresponding Author
ORCiD: https://orcid.org/0000-0003-4370-0544

Scott Phillips
Washington Poison Center

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Abstract
Background Abdominal pain may be a presenting symptom of lead poisoning, and is often difficult to diagnose. We aimed to determine the prevalence of abdominal pain in patients seen in the Laghman Hakim Hospital ED and GI clinic who were lead-intoxicated, with or without opiate use disorder.

Methods Between July 2017 and January 2018, patients seen in the ED and GI clinic of Loghman Hakim Hospital with unexplained abdominal pain or abdominal pain resistant to treatment were enrolled. Informed consent was obtained from potential enrollees. For standardization, a pre-designed data collection tool was developed for uniform data acquisition. Opiate use was determined historically. For this study, lead poisoning was defined as a blood lead level (BLL) greater than or equal to 30 μg/dL (1.45 micromoles/L) with concomitant GI symptoms.

Results Of 125 patients admitted, 28 (22.4%) had BLLs higher than 30 μg/dL. None of the patients had signs and symptoms of opioid withdrawal syndrome during evaluation. Elevated BLLs were significantly correlated with oral opium use/abuse, history of addiction for over the preceding 12 years. The daily opium use was more than 2.75 grams. There was a statistical correlation between lead toxicity and abdominal pain consistency and intensity, constipation, and paresthesias. Anemia, leukocytosis, and abnormal liver enzyme tests were laboratory findings associated with lead toxicity. Four patients died, one of whom was diagnosed with lead toxicity.

Conclusion Lead toxicity should be considered in the potential differential diagnosis of severe and resistant abdominal pain in patients referring to general EDs or GI clinics if a positive history of opium abuse exists.

Background
Acute abdominal pain is one of the leading reasons for seeking medical care in emergency and outpatient departments [1]. Abdominal pain has a diverse diagnostic schema, which ranges from mild self-limiting conditions to life-threatening emergencies. It is believed 20–40% of abdominal pain etiologies remain unknown at the time of discharge [2]. Lead toxicity is on the differential diagnosis for abdominal pain. The United States Centers for Disease Control and Prevention (CDC) suggests that blood lead levels (BLLs) of greater than 5 mg/dL are elevated.
Lead poisoning may occur from many situations, including occupational exposure (e.g., battery manufacturing workers, lead solder workers, automobile radiator repair, etc.) [3], tile workers [4], and potters [5] or paint chips [6]. Lead-based paints before 1950, old pipes, house dusts, imported toys, and herbal and Ayurvedic medications are among the possible sources for lead poisoning [7]. Lead poisoning is generally asymptomatic; however, it can present with abdominal pain, constipation, anemia, hearing loss, fatigue, neuropathy and neurotoxicity, encephalopathy, renal diseases, abortions, osteopenia, and even death.

Treatment of lead poisoning is centered on prevention with the eliminating lead exposure, proper diet (rich in calcium and iron), educating individuals, and if indicated, using chelating agents including (dimercaprol (BAL), calcium disodium ethylenediaminetetraacetic acid (CaNa2 EDTA), succimer (DMSA, 2–3 mesodimercaptosuccinic acid), and D-penicillamine) [8, 9].

Prevalence of lead poisoning has dropped over the recent years because of the lead safety and preventive measures and programs [10] although epidemics of lead poisoning due to adulterated opium or herbal medicine were recently reported worldwide [11, 12].

In 2016, an epidemic of lead poisoning occurred in Iran due to consumption of lead-contaminated opium. Some estimates of the size of the outbreak to involve more than 4,0000 people [11]. Abdominal pain is a well-known albeit infrequent symptom of lead poisoning [12-15], which has historically resulted in unnecessary diagnostic and even therapeutic procedures. Some may undergo unnecessary surgery to seek for possible intra-abdominal pathologies because the theaters (mostly gastroenterologists and surgeons) may not be familiar with lead-contaminated opium in their patients [16].

We studied patients in our emergency department (ED) and gastrointestinal (GI) diseases clinic for abdominal pain to determine the frequency of lead poisoning as a possible cause of their symptoms. Both inpatients and those who were managed as outpatients were evaluated. A major focus of this study was to examine possible factors that may correlate with lead poisoning. A listing of signs and symptoms noted in our cohort with abdominal pain were recorded that may also be related to lead poisoning.
Methods
A prospective, non-randomized, observational study was conducted between July 2017 and January 2018. Patients evaluated in the emergency and GI outpatient clinic with the chief complaint of abdominal pain of unknown origin or resistant to routine antacid treatment were enrolled into the study. Patients were considered as being lead-poisoned if their BLL was more than 30 µg/dL in conjunction with abdominal pain. Patients were informed of study details and voluntarily participated after providing informed consent. A predetermined study questionnaire was designed for this study. In the questionnaire, the patients were asked about their demographics, the quality/ location/ time of initiation and severity of their abdominal pain, previous history of abdominal pain and any given treatment or diagnostic procedures performed for pain management, prescriptive medication use, particular eating habit, herbal medicine consumption, previous history of lead toxicity, history of addiction, route and daily amount of the opium use, duration of addiction, and on-presentation signs and symptoms other than abdominal pain. Presenting laboratory testing, primary and final diagnoses, treatments performed, duration of hospitalization, need for ICU admission, and standard questions determining whether the patient is a user of opium (based on ICD criteria) including their history of substance abuse, gradual increase of drug consumption, unsuccessful tries to quit drug consumption, possible damaged social life because of drug addiction, excessive eagerness for taking drug, continuing use of drug even after being aware of its side effects, presence of withdrawal signs during its discontinuation, etc. were also asked and recorded. Laboratory tests including blood biochemistry and liver function tests were also collected. Capillary blood lead levels were checked by Lead Care II device using voltametry method. This device determines the BLLs between 3.2 to 65 µg/dL [18]. The levels below and above these limits are determined as “low” and “high” levels. For those with “low” results, a mean of 1.6 µg/dL was determined to be used in data analysis. For any level above 65 µg/dL, the number 65 was inserted into the statistical package for social sciences (SPSS) file (version 24) and data was analyzed. Quantitative variables were described based on their pattern of distribution, normal and non-normal, with mean and median in addition to their interquartile range and minimum to maximum ranges.
Kolmogorov-Smirnov test was conducted on the quantitative variables to determine their distribution (normal or non-normal). Continuous variables were compared between two groups of patients with normal and abnormal BLLs using t-test and Mann-Whitney U Test. For the factors that showed significant correlations, cut-off points with highest amounts of sensitivity and specificity were determined by using ROC Curve test. Evaluation of categorical variables was done by conducting Chi square test. P values less than 0.05 were considered to be statistically significant. 95% confidence intervals and odds ratios were demonstrated for showing the power of association. Multivariable analysis was conducted by defining logistic regression models.

Sample size

Considering the previously performed pilot study on 93 patients which showed an average frequency of BLLs higher than 10 µg/dL to be about 47.3% [18], the desired 95% level of confidence, and the desired ± 1.8 µg/dL accepted margin of error, a sample size of 142 was determined. Sixty-seven patients were expected to have BLLs higher than 10 µg/dL.

Results

Data on one hundred twenty-five patients was collected. Of the 125 cases, 62 (49.6%) were seen in the ED and 63 (50.4%) were seen in outpatient GI clinic. Almost 80% of the patients were male. When the final diagnosis of lead poisoning was confirmed, 27 out of 28 patients were men. Twenty-eight patients (22.4%) had BLLs higher than 30 µg/dL and 64 and 108 patients had BLLs above 10 µg/dL and 5 µg/dL, respectively.

Four cases died, one of whom was diagnosed with lead poisoning and had died due to aspiration pneumonia. Other causes of death were gastrointestinal bleeding, opioid overdose, and congestive heart failure. In 83 (66.4%) patients, there was a positive history of opium dependence. All 28 patients with confirmed lead poisoning had the history of addiction and 15 (53.8%) received chelating agents. Demographic data and lab test results are summarized in Tables 1 and 2. In the patients with high BLL, four patients underwent aggressive procedures (colonoscopy and endoscopy) to rule out severe background causes of abdominal pain. None of our patients underwent a surgery. Table 3 illustrates the cofactors which showed significant correlation with lead poisoning. In the multivariate
analysis, among the factors that showed univariate correlation with elevated BLL with few missing data, only constipation (OR 8.9 CI 95% 1.3–59.3) and leukocytosis (OR 12.6 CI 95% 1.7–95.6) were significantly related to high BLLs. Multivariate regression information has been summarized in Table 4.

Discussion
In this study, all 28 patients with confirmed diagnosis of lead poisoning also had a history of opium addiction and opiate use disorder (OUD). Although some patients were polysubstance users, all poisoned patients had the history of OUD. There was no significant correlation between consumption of herbal medicines, eating habits, and occupation and lead poisoning as many of our patients had jobs that did not predispose them to lead exposure. This suggests adulterated opium as the main source of lead poisoning. Patients who took daily amounts of more than 2.75 grams of opium had a 5.2-time greater risk of development of lead poisoning. There was also a correlation between lead poisoning and OUD in this study. Persons continued to abuse opium after being aware of its consequences although this correlation was not statistically significant. This may be due to the fact that this innate feeling will result in taking greater amounts of opium. We also detected a link between the duration of addiction and lead poisoning.

Before analysis, it was presumed that patients’ dependence on opium and their tendency to continue opium even after being aware of its consequences would correlate with daily amount of opium intake. However, statistical analysis did not show an association. This may be due to an inaccurate history of daily opium intake.

Significant difference in gender and lead poisoning in this study was found. In this cohort, 83 patients with positive addiction history were male, 78 males and five females. This may demand further evaluation of role of gender in development of lead poisoning.

In our study, there was a significant correlation between lead poisoning and lab tests. In the poisoned group, anemia (Hb<13 mg/dL) was 6.3 times more common compared to the normal group. Simultaneous presence of lead poisoning and anemia has also been mentioned in the previous studies. Lead interferes with the production of heme [18–21]. In fact, during the heme production, two
pivotal enzymes (5-aminolevulinic acid dehydratase and ferrochelatase) are inhibited [22,23]. There was also a connection between BLL and RBC count which is similar to the results withdrawn by previous authors [22,23]. Terayama suggested that lead exposure would result in cell membrane changes that reduced the lifetime of erythrocytes [23]. In addition, lead is linked with lower level of erythropoietin [24] both of which mechanisms can cause a reduction in RBC count. Decreased amounts of erythropoietin, decreased RBC life span, and deformability besides the decrease in heme production justify the correlation of decreased hematocrit and higher BLLs.

There was also an association between platelet (PLT) count and BLL. In some previous studies, BLL was associated with decreased platelet count [25] while in some others, increased PLT number has been mentioned [26]. However, complete blood count (CBC) profile of our patients demonstrated a higher PLT count in lead-poisoned patients. It has also been mentioned that the risk of stroke is higher in the patients with abnormal BLL [27]. Higher PLT numbers in these patients can be a potential explanation for this finding.

WBC count more than 9050 per mm$^3$ had an 8.1-time higher frequency of lead poisoning. Similar findings have been reported by Katavolos et al in 2007 [26]; however, they considered leukocytosis as an accidental finding. Paucity of studies in this field warrants further studies to elucidate the association between higher BLL and leukocytosis.

As Mirzaei et al declared in 2018 [27], paresthesia was associated with lead poisoning. Presence of paresthesia is due to the neuropathic effects of lead. Typically, lead firstly involves the motor nerves of wrists and finger extensors and then spreads to other muscles [28]. Several explanations have been given for neuropathic effects of lead. Impaired Ca$^{2+}$ hemostasis due to lead exposure will result in nerve apoptosis [29]. Lead also disrupts the fluid normal hemostasis in neurons which results in high cellular pressure and consequent segmental demyelination in neurons [30].

We also found a significant correlation between constipation and lead poisoning as one of the main manifestations of this toxicity. As mentioned earlier, there was also statistical correlations between lead poisoning and pain consistency and severity. Lead can cause abdominal pain through several mechanisms. Lead will negatively affect the motility of intestines [31]. It can be due to the effect of
lead on intestinal neural web or on smooth muscles. It can also be due to the increase in δ aminolevulinic acid (a porphyrin precursor) as a result of induced porphyrinopathy by lead poisoning [32]. There is also evidence for the role of lead in acute pancreatitis. Lead also interferes with sodium transporter channels of the intestine. These mechanisms explain the causality of lead in abdominal pain but the question that can be raised here is how can lead toxicity be differred from opium withdrawal syndrome or narcotic bowel syndrome especially regarding to the fact that all of the cases in this study were due to adulterated opium. Characteristics of opioids withdrawal syndrome (OWS) and narcotic bowel syndrome (NBS) is listed in Table 5 [33, 34]. Since the main concern of this was to focus on the presence of lead poisoning in individual seeking medical care with unknown or treatment resistant abdominal pain, patients that clearly showed such conditions were not enrolled. Another prominent factor which significantly correlated with lead poisoning was abnormal liver enzyme tests possibly due to oxidative/antioxidant cycle disturbances in the liver tissue [35] or depletion of the antioxidants savings of the cells [36]. Three out of 21 patients who had primarily unjustified abdominal pain and three of those 24 who were diagnosed primarily with GI problems were lead-poisoned. Paying attention to lead poisoning as a potential diagnosis could rule out the need for invasive procedures like colonoscopy and endoscopy. Although none of our lead-poisoned patients had undergone surgery before the diagnosis, the possibility of this diagnosis during handling acute abdomen should always been borne in mind.

Conclusion
Lead poisoning should be considered as a potential diagnosis in patients with positive history of opium or ayurvedic medicine intake; however, differential diagnosis of lead poisoning in abdominal pain should be correlated with local epidemiologic data on lead poisoning.

LIMITATIONS
Our study was conducted at the time of the outbreak of lead poisoning due to adulterated opium. This will explain relatively high numbers of patient with lead toxicity. Almost half of our cases were patients to whom we had limited access after their discharge and this issue caused relatively high amount of missing data especially in laboratory findings in our study. Some patients did not even
return for treatment causing almost 45 missing data in treatment information. We believe they just discontinued using opium but this is another limitation of this study. Another aim was to determine the districts in Tehran with most prevalence of dealing with adulterated opium with lead; however, because of the paucity of cases this could not be done.

List Of Abbreviations

BLL = Blood Lead level, CBC = Complete Blood Count; CI = Confidence Interval; ED = Emergency Department; GI = Gastrointestinal; ICD = International Classification of Disease; ICU = Intensive care Unit; NBS = Narcotic Bowel Syndrome; OR = Odds Ratio; OUD = Opiate Use Disorder; OWS = Opioids Withdrawal Syndrome; PLT = Platelet; SPSS = Statistical Package for Social Sciences

Declarations

Ethics approval and consent to participate: This study approved by Shahid Beheshti University of Medical Sciences ethics committee (IR.SBMU.RETECH.REC.1397.557). The informed consent obtained from study participants was written.

Consent to publish: Available.

Availability of data and materials: The data is all presented in the text.

Competing interests: None.

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Authors’ Contributions: HHM is the guarantor of integrity of the entire study. MR and MS gave the study concepts and designed the study. SKH, NZ, and PP did the literature research. SKH and HM performed the data analysis. SKH and HHM performed the statistical analysis. NZ, SKH, MS, HM, PP and HHM prepared the manuscript draft and PS did edit the final manuscript. All authors have read and approved the manuscript.

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Tables

Table 1: Patients’ demographic characteristics (n=125)

|                           |                                             |
|---------------------------|---------------------------------------------|
| **Age; mean (range)**     | 48±16.9 (16 to 85)                          |
| **Gender (M/F)**          | 100/25                                      |
| **Inpatient/outpatient**  | 62/63                                       |
| **Addiction history**     | 83 (66.4%) with positive addiction history |
| **Treatment**             | 16 received chelating agents (12.8%), 62 (49.6%) were treated conservatively, 2 underwent surgery (1.6%), 45 missing (36%) |
| **Outcome (death/recovery)** | 4/121                                      |

Table 2: On-presentation lab tests

|                                | Patients with BLL≤ 30 mg/dL N=97 | Patients with BLL≥ 30 mg/dL N=28 | P value | Total N=1 |
|--------------------------------|----------------------------------|----------------------------------|---------|-----------|
| **WBC count median (min-max)** | 7800 3200-23000 6700-9375         | 12.100 5100-25800 8800-13700      | 0.000   | 8400 3200-6800 |
| **The HCT median (min-max)**   | 39 10-50.70 36.975-42.050         | 35.10 22.5-44.20 29.300-38.850    | 0.001   | 38.5 10.0-35.1 |
| **RBC median (min-max)**       | 4.435 1.10-6.29 3.9575-4.9000     | 4.160 2.60-5.32 3.320-4.500       | 0.016   | 4.33 1.10-3.90 |
| **Hgb median (min-max)**       | 13.8 3-17.20 12.1250-14.6750      | 11.70 7.40-15.20 9.600-13.00       | 0.000   | 13.00 3.00-11.7 |
| **MCV median (min-max)**       | 87.00 61.50-116                   | 87 77-95.71                       | 0.756   | 87 61.5   |
| Test       | Median (min-max) | Interquartile range | Mean ± SD (min, max) | ESR median (min-max) | CRP median (min-max) | Amylase median (min-max) | Lipase median (min-max) |
|------------|------------------|---------------------|----------------------|---------------------|---------------------|--------------------------|--------------------------|
| LDH        | 396 (30-2108)    | 84-89               | 462 (299-890)        | 0.023               | 415 (30-2)          | 415 (30-2)                | 415 (30-2)                |
|            | 327.5-560        |                     | 414.5-610.250        |                     |                     |                          |                          |
| PLT        | 201.50 (61-540)  | 209 (61-5)          | 242 (98-435)         | 0.013               | 209.50 (61-5)       | 209.50 (61-5)             | 209.50 (61-5)             |
|            | 176.5-242        |                     | 185.250-306.00       |                     |                     |                          |                          |
| AST        | 20 (10-469)      | 22 (10-4)           | 34 (12-197)          | 0.000               | 21 (10-4)           | 21 (10-4)                 | 21 (10-4)                 |
|            | 14-30            |                     | 23.250-60.50         |                     |                     |                          |                          |
| ALT        | 19 (10-1122)     | 21 (10-1)           | 36 (12-219)          | 0.003               | 21 (10-1)           | 21 (10-1)                 | 21 (10-1)                 |
|            | 15-27            |                     | 19.25-68             |                     |                     |                          |                          |
| BS         | 103 (49-368)     | 109 (49-3)          | 123 (95-367)         | 0.001               | 109 (49-3)          | 109 (49-3)                | 109 (49-3)                |
|            | 91.5-123         |                     | 111-168              |                     |                     |                          |                          |
| BUN        | 28.5 (10-204)    | 30 (10-2)           | 30 (12.5-131)        | 0.342               | 30 (10-2)           | 30 (10-2)                 | 30 (10-2)                 |
|            | 20-40.8          |                     | 23-43                |                     |                     |                          |                          |
| Cr         | 1.1 (0.7-3.40)   | 1.10 (0.7)          | 1.090 (0.7-1.30)     | 0.495               | 1.10 (0.7)          | 1.10 (0.7)                | 1.10 (0.7)                |
|            | 0.9-1.2          |                     | 1.00-1.10            |                     |                     |                          |                          |
| Na         | 139.50 (125-145) | 139 (125)           | 137 (130-148)        | 0.038               | 139 (125)           | 139 (125)                 | 139 (125)                 |
|            | 138-142          |                     | 135-140              |                     |                     |                          |                          |
| K          | 4.05 (3.20-5.0)  | 4.1 (3.2)           | 4.2 (3.40-4.80)      | 0.295               | 4.1 (3.2)           | 4.1 (3.2)                 | 4.1 (3.2)                 |
|            | 3.7-4.30         |                     | 4.00-4.30            |                     |                     |                          |                          |
| ESR        | 6 (1-51)         | 8.5 (1)             | 21 (3-86)            | 0.034               | 8.5 (1)             | 8.5 (1)                   | 8.5 (1)                   |
|            | 2.00-15          |                     | 8.5-45.5             |                     |                     |                          |                          |
| CRP        | 7 (0.20-155)     | 7 (0.2)             | 6.850 (0.2-96.50)    | 0.934               | 7 (0.2)             | 7 (0.2)                   | 7 (0.2)                   |
|            | 3-41             |                     | 1.375-77.25          |                     |                     |                          |                          |
| Amylase    | 62 (11-293)      | 58 (11-2)           | 53 (16-102)          | 0.405               | 58 (11-2)           | 58 (11-2)                 | 58 (11-2)                 |
|            | 42-76            |                     | 31-91                |                     |                     |                          |                          |
| Lipase     | 29 (16-103)      | 28 (9-11)           | 21 (9.00-114)        | 0.406               | 28 (9-11)           | 28 (9-11)                 | 28 (9-11)                 |
|            | 20-37            |                     | 20.00-37.00          |                     |                     |                          |                          |
|                      | P value | Odd ratio | Confidence interval |
|----------------------|---------|-----------|---------------------|
| Addiction history    | 0.000   | 1.428     | 1.276               |
| Gender (male/female) | 0.014   | 0.113     | 0.015               |
| Pain type (colic pain - constant pain) | 0.024 | 2.744 | 1.119 |
| Pain duration (LESS OR MORE THAN A WEEK) 64 sensitivity 64 specificity | 0.010 | 3.278 | 1.302 |
| Ingestion of opium (as the way for taking drug) | 0.001 | 16.059 | 2.026 |
| Condition                                                                 | p-value | Odds Ratio | 95% CI     |
|---------------------------------------------------------------------------|---------|------------|------------|
| Duration of addiction (more than 12 years)                               | 0.039   | 2.720      | 1.037      |
| Abnormal AST test                                                        | 0.003   | 4.911      | 1.636      |
| Abnormal ALT test                                                        | 0.000   | 6.875      | 2.309      |
| Leukocytosis                                                              | 0.000   | 8.095      | 3.043      |
| RBC Count                                                                 | 0.042   | 2.547      | 1.017      |
| Hematocrit                                                                | 0.001   | 4.622      | 1.809      |
| Platelet count                                                            | 0.001   | 4.819      | 1.822      |
| ESR                                                                       | 0.02    | 7.000      | 1.200      |
| LDH                                                                       | 0.002   | 7.813      | 1.947      |
| Na                                                                        | 0.011   | 3.584      | 1.301      |
| Blood sugar                                                               | 0.002   | 5.051      | 1.747      |
| Anemia                                                                    | 0.000   | 6.253      | 2.175      |
| Constipation                                                              | 0.000   | 7.464      | 2.320      |
| Paresthesia                                                               | 0.002   | 7.455      | 1.725      |
| Continuous using of opium even with being aware of its side effects       | 0.031   | 5.031      | 1.041      |
| Excessive eagerness to use opium                                          | 0.038   | 3.694      | 1.091      |
| Daily amount of opium intake (more than 2.75 gr)                         | 0.005   | 5.257      | 1.577      |

Table 4. multivariate regression
|                      | P value | OR           | CI 95 % (upper – lower) |
|----------------------|---------|--------------|------------------------|
| Addiction history    | .998    | 295607633.200 | .000                   |
| Gender               | .809    | .645         | .018                   |
| Pain type (colic/constant) | .656    | 1.458        | .278                   |
| Pain Duration        | .496    | 1.760        | .346                   |
| leukocytosis         | .014    | 12.609       | 1.662                  |
| RBC count            | .979    | 1.029        | .113                   |
| HCT                  | .942    | .910         | .071                   |
| PLT                  | .277    | 2.775        | .441                   |
| Anemia               | .111    | 7.386        | .632                   |
| constipation         | .024    | 8.885        | 1.330                  |
| paresthesia          | .097    | 8.611        | .680                   |

Table 5: Characteristics of opioid withdrawal syndrome (OWS) and narcotic bowel syndrome (NBS)

| OWS                      |                          |
|--------------------------|--------------------------|
|                          | lacrimation or rhinorrhea, piloerection "goose flesh," myalgia, diarrhea, nausea/vomiting, pupillary dilation and photophobia, insomnia, autonomic hyperactivity (tachypnea, hyperreflexia, tachycardia, sweating, hypertension, hyperthermia), and yawning. |

| NBS                      |                          |
|--------------------------|--------------------------|
|                          | constipation, nausea, bloating, ileus and predominantly abdominal pain |