Practical Guidelines for Evaluating Lead Exposure in Children with Mental Health Conditions: Molecular Effects and Clinical Implications

Mary G. Burke, MD1
Mark D. Miller, MD, MPH2

1Sutter Pacific Medical Foundation, Greenbrae, CA; Pediatric Environmental Health Specialty Unit, University of California, San Francisco, San Francisco, CA; 2Director, Pediatric Environmental Health Specialty Unit, University of California, San Francisco, San Francisco, CA

Abstract: Children in the United States are exhibiting extremely high levels of attentional and learning disabilities. Although lead has been eliminated from many industrial products, children continue to come into contact with it, such as in toys and cosmetics. Lead exposure occurs most commonly in poor, urban populations, and can exacerbate psychiatric disorders associated with stress. We present 1) an overview of lead exposure; 2) a detailed summary of current research on the molecular synergy of toxicity caused by lead and stress; 3) a review of human studies that appear to correlate with these molecular findings, including understanding nutrition, environmental enrichment, and caregiving as risk modifiers; and 4) a systematic approach for mental health practitioners in managing children presenting with multiple symptoms and risk factors for mental health conditions. In this article, we review some of the clinical and scientific challenges that relate to the assessment and treatment of children presenting for mental health care who may have potential lead exposure.

Keywords: lead; pediatric mental health; developmental psychopathology; environment

Background
The United States is seeing an unprecedented increase in the diagnosis of attentional and learning disabilities, with 16% of children in this country now experiencing these disabilities.1 One percent of all children and 1.4% of all boys have an autistic spectrum disorder.2 Researchers have observed that many of these children receive mental health treatment without accurate assessment of the developmental disorder.3 Epidemiological and molecular data indicate that chemical toxins, developmental stresses/deprivation, and genetic susceptibility interact to produce adverse psychiatric outcomes in children.4–7 In this article, we review some of the clinical and scientific problems that relate to the assessment and treatment of children presenting for mental health care who may have potential lead exposure. Multiple studies have pointed out that even when lead levels are < 10 µg/dL, children remain at risk for sequelae of neurotoxic exposure.8,9 Addressing the role of lead in developmental psychopathology is important because of a large gap between recommendations and practice, despite a vast amount of data and accepted screening and treatment guidelines. The National Health and Nutrition Examination Survey (NHANES) III found that only 43% of children aged > 1 year, who were enrolled in Medicaid and who had elevated blood lead levels (BLL), had previously been tested for lead exposure.10 Few mental health clinicians routinely consider lead exposure in the differential diagnosis of children with attentional or behavioral disorders11 despite Centers for Disease Control and Prevention (CDC) recommendations.12

From a bioethical standpoint, lead exposure tends to be highest in urban and poor communities,9,10 occurring in children already exposed to high numbers of psychosocial
stressors. Current data indicate that lead, violence, and stress co-occur epidemiologically, and overlap in their molecular effects on those systems of the brain involved in learning, impulse control, fear response, and aggression.13–18 This article, a joint project of the University of California, San Francisco Pediatric Environmental Health Specialty Unit and the Collaborative for Health and the Environment’s Mental Health Initiative, presents recommendations for lead screening guidelines. We propose that the integration of mental and environmental health care will improve treatment, and address the substantial gap between children of high and low socioeconomic status in developmental outcomes.

Methods

We describe a bioecological framework for understanding lead exposure in children, and outline a comprehensive, multi-level approach to children presenting with behavioral disorders, history of significant psychosocial stress, and possible toxic lead exposure. As noted, children born into poverty are exposed to the highest number of both social stressors and chemical toxins, and have the least access to potentially protective factors.19 Although lead levels have declined dramatically overall in the United States during previous decades, NHANES found that 14% of non-Hispanic black children have BLLs between 5 and 10 µg/dL, compared with 4.2% of non-Hispanic white children.10 The CDC and the American Academy of Pediatrics have stated that “no threshold for the toxic effects of lead has been identified.”12,20 Epidemiologically, this means that a meaningful percentage of our children have an a priori risk for lowered intelligence quotient (IQ) and lowered potential regardless of other factors. Lead has been conclusively linked with declines in IQ,8,21,22 and it is one of many components of low socioeconomic status that adversely affect children’s developmental and health outcomes.9

Poor, urban, minority children are additionally exposed to multiple other stressors. These include “social toxins” (ie, exposure to community and/or family violence, discrimination, decreased access to health care, and diminished access to mitigating resources, such as recreational facilities or nutrition)23 as well as other toxic risks, such as close proximity to freeways or industrial pollutants.10 A recent review concluded that lead exposure accounted for 1% to 4% of variance in cognitive ability, while social and parenting factors accounted for 40%.24 As we discuss below, adverse social circumstances and toxic exposures tend to magnify each other. Current public health approaches to this network of risk and protection use a systems model to understand the impact of stressors and protective factors on individuals and communities.7,23,25 Such “bioecological models”26 propose:

The scientific study of the progressive, mutual accommodation, throughout the lifespan, between a growing organism and the changing environment in which it lives...The ecological environment is conceived...as a nested arrangement of structures, each contained [and influencing] the next....27

Within this model, the following observations pertain to the study of toxic exposure:

1. Risk is transmitted across generations. For example, maternal body burden of stored lead is released into fetal circulation during pregnancy,28,29 maternal care in infancy has strong, lasting impacts on the infant’s arousal system,30 and quality of the home environment strongly predicts vulnerability to lead toxicity.24,31

2. Early stress may predispose the person to later-onset disease through reduction in capacity to withstand later stress or to abnormal adaptation required to survive the early insult.32 The concept of allostasis (ie, the molecular adaptation to stress to allow survival) underlies this observation.33,34

3. Patterns of alterations in the hypothalamic-pituitary-adrenal (HPA) axis, the hippocampus, and other neurologic and hormonal systems can now be demonstrated in animals exposed to lead, stress, or both. Molecular events related to multiple early toxic and stressful exposures may amplify their impact on the developing nervous system. This may be especially true of lead, which has been specifically linked to abnormalities in the hippocampus and the HPA axis.15,16 In particular, both early lead exposure and early life trauma predispose the developing child to aggressive or fearful responses to novelty or stress, and enhance impulsivity.

Overview of Lead Exposure

Lead is a ubiquitous, naturally occurring metal that has been in use since ancient times for cosmetics and manufacturing. Lead in gasoline was banned in the United States in the 1970s, but continues to be present in many developing countries. Lead was banned from house paint in 1978, but is widely used in industrial manufacturing, and continues to be found in dust and paint in and near old housing and businesses. Common industrial sources of lead in the local environment include smelters, battery manufacturers, waste-treatment plants, and the automotive and aeronautical industries.35 Children may be exposed (orally, transdermally, or through inhalation) to lead in dust or soil, ceramics, toys, jewelry,
Lead Exposure and Pediatric Mental Health

Lead is carried in the blood stream throughout the body, primarily by red blood cells. It is avidly taken up by mineralizing tissues such as bone and teeth, but also deposits in muscle and other protein-based organs. Lead is eliminated from the blood in 28 to 36 days. Blood lead levels primarily indicate recent exposures, although current evidence indicates that BLLs may be due to internal leaching as well as external sources. Lead is excreted primarily by the liver into the feces via the bile, but is also excreted by the kidneys. High or chronic doses can cause renal accumulation and kidney damage.

Lead stored in bone is inert, but can be released in times of “calcium stress,” such as pregnancy and lactation (thus putting the fetus or infant at increased risk of exposure), menopause, or in chronic disease states (eg, in patients with kidney failure, hyperthyroidism, or in calcium-deficient patients). Calcium supplements reduce leaching, decreasing blood levels.

Lead readily crosses the placenta and enters the fetal brain. Lead not only crosses the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier easily, but it may also weaken them, augmenting damage from lead or other toxins. Robust evidence has shown that prenatal lead exposure is linked to IQ deficits and symptoms of attention-deficit/hyperactivity disorder. Intrauterine exposure disrupts normal neuronal migration by preventing normal cellular adhesion, leading to abnormal brain circuitry. Researchers have consistently identified associations of modestly elevated BLLs (5–10 µg/dL) with aggression, delinquency, and neurological “soft signs” and more recently with depression and anxiety. Early lead exposure has also been linked in laboratory and epidemiological studies to adult diseases, such as hypertension and heart disease, kidney disease, osteoporosis, and Alzheimer’s disease. In summary, there is no “behavioral profile” for lead exposure, but it is implicated in multiple psychiatric illnesses.

Toxicologically, lead influences a number of molecular processes. Thematically, its effects stem from 2 main characteristics: 1) it is a divalent cation (Pb²⁺), thus acting as a competitive agonist or antagonist for naturally occurring cations, most significantly calcium (Ca²⁺), but also zinc (Zn²⁺); and 2) it bonds covalently with amino acids containing sulfhydryl, amine, phosphate, and carboxyl groups. These implicate lead in the following processes: abnormal patterns of DNA replication, mediated by methylation (inactivation) or by activation via protein kinase C (PKC) and other messengers; the generation of reactive oxygen species (ROS); the abnormal activation or inactivation of enzymes, or the alteration of proteins; abnormal development of neuronal receptors, in particular glutamate; abnormal levels of other neurotransmitters; and abnormal activation of the HPA axis, leading to disruptions in multiple neurotransmitter and neuroendocrine systems. These mechanisms tend to converge on several pathways, as will be discussed below.

As a calcium mimic, lead readily crosses the BBB, and subsequently also damages the blood-CSF barrier. The potent neurotoxicity of lead is explained by this capacity, by the high number of potential receptor sites for lead in the brain, and by the sequestration of lead by astrocytes. While sequestration initially protects the neuron, the astrocytes can then serve as a reservoir of lead contributing to low-level exposure later. In vitro and animal studies have clarified the following mechanisms of lead toxicity.

Epigenetic Effects

The timing of DNA methylation (gene silencing) is crucial during early development, as the brain must unfold in a carefully timed sequence. Thus, early toxic exposures that disrupt DNA activation patterns have possible long-term consequences. Researchers have demonstrated that primates and rodents exposed prenatally to lead have an increased rate of amyloid plaques as adults. Exposed rats show an early, excessive activation of the gene coding for amyloid precursor protein (APP), the protein linked to abnormalities in Alzheimer’s disease. This activity ceases in adulthood, but increases again in senescence. Monkeys in late adulthood that were exposed prenatally had increased APP mRNA levels and decreased markers for DNA methylation, which is a sign of excess DNA replication. This group of monkeys also had increased oxidative damage to brain tissue. This suggests that early lead exposure predisposes the animal to late life disease. A study of human infants found that BLL in cord blood was inversely related to DNA methylation. This group of children has not yet been followed into adulthood but are theoretically at risk for late-onset disease based on the animal studies.
Oxidative Stress

Another potent action of lead is on heme synthesis, where it inhibits the activity of delta-aminolevulinic acid (ALA) dehydratase (an enzyme that converts ALA to porphobilinogen) and inhibits ferrochelatase (an enzyme downstream in hemoglobin production). A feedback loop increases the activity of ALA synthetase; more ALA is produced, but it accumulates in the blood. Aminolevulinic acid has been linked to the accumulation of ROS and oxidative stress. Chronic lead exposure can cause hypocromic anemia, usually normocytic or microcytic. Because of its avid protein binding, lead also damages antioxidant enzymes, as well as the important antioxidant molecule glutathione. As a competitor of zinc, lead is incorporated into and disrupts the function of metallothionein, another important antioxidant molecule. Other heavy metals, including cadmium and mercury, also have this mechanism of toxicity. Lead thus both increases ROS, while diminishing the cell’s capacity for reduction. In addition, increased levels of ALA have been shown to decrease the function of the neurotransmitters gamma-aminobutyric acid (GABA), serotonin, and acetylcholine, which are important in psychiatry as they regulate anxiety, memory, attention, and mood.

Calcium-Mediated Toxicity

Because lead acts as a calcium agonist, it disrupts the tight regulation of intracellular calcium. This is significant for general cell function, and for learning, a cellular process dependent on glutamate and the NMDA receptor. In the first case, an increase in intracellular Ca\(^{2+}\) is the first step in the activation of a number of intracellular enzymes, including PKC. This enzyme in turn initiates vital cell functions, including DNA synthesis, for proteins responsible for neuronal development and differentiation. Lead disrupts membrane integrity, possibly through peroxidation and damage to the function of the Ca\(^{2+}\) channel. In the mitochondria, lead interferes with the generation of adenosine triphosphate and reduction of ROS generated by normal function (e.g., the electron transport chain). Membrane and mitochondrial damage lead to increased intracellular calcium levels and increased ROS. High levels of intracellular Ca\(^{2+}\) then cause cellular damage through multiple pathways, ending in apoptosis (cell death programmed by the genome, initiated by PKC) and necrosis (nonspecific cell death via membrane disruption, cytoskeletal damage, and mitochondrial injury).

Lead disrupts the normal development and function of the NMDA receptor, a 2-unit glutamate receptor that is located at different sites of the brain, including the cortex and the hippocampus. Glutamate acts in conjunction with calcium as a neurotransmitter at the hippocampus to allow the special type of learning called long-term potentiation. However, excess glutamic acid in the synapse causes excitotoxicity, and can lead to apoptosis.

The take-away message for clinicians is that lead disrupts the delicate balance of release and uptake that governs glutamate levels in the central nervous system, leading to abnormal structure and function of the hippocampus, and to excitotoxicity and apoptosis. Excitotoxicity has been linked to fetal exposure to alcohol and other drugs of abuse, and may be a central factor in schizophrenia. Early lead exposure has been shown to sensitize rodents to the activating and reinforcing effects of stimulant drugs of abuse.

Effects on the Stress-Response System

Lead appears to be a potent actor on the HPA axis, especially through intrauterine exposure. It is now canonical in psychiatry that early life experiences, including quality of mothering and exposure to maltreatment, affect the developing child’s reactivity to stress via the HPA axis. In particular, early nurturing—including soothing physical contact and sensitive caregiving—increases the number of glucocorticoid (GC) receptors in the brain, particularly in the hippocampus. The hippocampus gives inhibitory feedback to the HPA axis, and blunts the release of corticotropin in response to stress. The hippocampus is also an important site for learning and memory. Laboratory animals whose early lives are stressful are likely to have a higher circulating GC and adrenal hormones and more reactivity to novelty and stress. Brain plasticity (the capacity of the brain to remodel in response to new experiences) is greater in those individuals whose early life was less stressful. DNA methylation and the generation of ROS appear to be important mechanisms for these environmentally mediated changes. Fostering by highly nurturing rat dams and access to enrichment (increased socialization and self-directed exercise and exploration) reverses the molecular and behavioral effects of early life stress in rats. In human adults, the number of GC receptors has been linked to child...
abuse in one postmortem study, while measures of learning and memory impairment correlated in one study with physiological markers for oxidative stress.

Numerous laboratories are now demonstrating the synergistic effects of stress and lead in animals, as well as the benefits of enrichment. For example, rat pups who were exposed to lead in utero and subsequently raised in isolation have significant deficits in learning, which are eliminated in lead-exposed pups raised in an enriched environment. However, enrichment does not completely eliminate molecular changes wrought by prenatal lead exposure. Exposed, isolated pups have decreased brain-derived neurotrophic factor (BDNF), which is a key molecule for nerve growth and synaptic plasticity. Pups exposed but raised in an enriched cage have BDNF levels intermediate between exposed, isolated pups and nonexposed pups from an enriched cage.

Summarizing this work, animal studies show that being raised in an enriched environment—including high-nurturing parental behavior, and opportunities for self-directed learning and physical exercise—decrease the behavioral deficits and some of the brain deficits associated with early lead exposure. The opposite is true for animals raised in isolation, or exposed to either prenatal or early stress. These animals showed greater perturbations of the stress-response (HPA) system and of the memory system (the hippocampus).

Psychosocial Modifiers of Lead Effects in Humans

There are suggestive similarities between animal and human studies of early lead exposure. Several researchers have robustly demonstrated that psychosocial advantage is protective for children with increased BLLs, and may be the most important determinant of outcome in lead-exposed children who are below the CDC threshold of 10 µg/dL. Lead exposure is most detrimental to those with the least psychosocial protection. One study showed IQ deficits in children of low socioeconomic status beginning at 6 µg/dL, whereas high socioeconomic status children only displayed deficits at > 10 µg/dL. In children of high and low socioeconomic status with BLL > 10 µg/dL, the high socioeconomic status children displayed a steady recovery of IQ over time, while the low socioeconomic status children showed an equivalent decrease. Several studies have shown that a better score on the HOME inventory (a measure of parenting quality for families with infants and young children) is significantly protective of IQ in lead-exposed children, especially in children of low socioeconomic status.

Chemical and Nutritional Modifiers of Lead Toxicity

There are few studies of chemicals co-occurring with lead, but high levels of manganese increases lead deposition in rat brains, and studies of children have found worsened outcome per increase in BLL for those who had a co-exposure to high levels of this chemical. Nutritional deficits of calcium, zinc, and iron enhance lead absorption. Dietary calcium and iron protect against lead absorption in the gut. Rodent studies show that vitamin C, vitamin E, and thiamine protect against lead toxicity, while dietary folate and iron are protective in human children. Maternal diet and habits while pregnant have also been linked to BLLs, which in turn impact fetal lead exposure. One study found that lead levels were inversely related to maternal thiamine intake, serum folate levels, and were positively associated with cigarette and alcohol use, after controlling for sociodemographic variables. Serum cotinine level (a metabolite of nicotine) has also been proposed as exacerbating the risk of conduct disorder in children with increased BLLs.

Clinical Implications and Discussion

Clearly distinguishing and treating the multiple risk factors contributing to behavioral problems in a child with school failure, disruptive behavior, and lifetime exposure to multiple industrial contaminants or exposure to cigarettes or drugs of abuse may be impossible. However, it is possible to clarify these factors, and to address them methodically and perhaps sequentially, based on our judgments about acuity of presentation and costs and benefits of specific interventions.

Assessment

Developmental Screening

We recommend that mental health clinicians routinely include a developmental screen for children with behavioral disorders and learning or academic difficulties, where this has not been done previously. This screening can include a time-efficient parent questionnaire like the Parents’ Evaluation of Developmental Status (ages 0–9 years) or the Child Development Inventory (0–6 years). Clinician-administered screens require some additional time and training, but may be cost-effective in community settings where there is limited access to developmental pediatrics or psychological testing.
History

It is important to obtain an environmental health history for children with developmental disorders. Figure 1 offers a list of sources for history screening information and information about lead testing and exposure risks. Children who are at increased risk for lead exposure include those with the following history:

- Children with pica.
- Residence in housing built before 1978, or in a house that has been renovated.
- Proximity to industry, including battery manufacturing, smelting, mining, airports or freeways.
- Exposure to cosmetics or folk remedies from developing countries.
- Use of ceramics that are not guaranteed to be lead-free.
- Use of toy jewelry or painted toys that are not guaranteed to be lead-free.35,37

Family members can bring home lead dust on clothing. Occupations of residents in the home should be elicited for potential sources of lead (or other developmental toxins). Maternal exposure to lead while pregnant is one of the most important contributors to lead toxicity, even if current BLLs are normal.

Testing

Although pediatricians are generally familiar with testing guidelines, mental health clinicians may be unfamiliar with the guidelines. There are some settings where the psychiatrist may be the only physician seeing a child routinely, or where a primary care physician and non-physician professional must collaborate to provide psychiatric care. The most recent CDC guidelines state that a Medicaid-eligible child who meets any one of the following criteria should receive a blood lead screening test:61

- Child is suspected by a parent or a health care provider to be at risk for lead exposure.
- Child has a sibling or frequent playmate with elevated BLL.
- Child is a recent immigrant, refugee, or foreign adoptee.
- Child’s parent or principal caregiver works professionally or recreationally with lead.
- Child has a household member who uses traditional, folk, or ethnic remedies or cosmetics, or who routinely eats food imported informally (eg, by a family member) from abroad.
- Child’s family has been designated at increased risk for lead exposure by the health department because the family has local risk factors for lead exposure (eg, residence in a designated high-risk zip code or near a known point source).

All children eligible for Medicaid should be tested at 12 and 24 months; those who have not been previously tested should be tested between 36 and 72 months. Targeted screening should be done for previously untested children with histories suggesting exposure.37 Some regions have specific guidelines available through the CDC. The CDC
the CDC, chelation is indicated only for levels above 45 \( \mu \text{g} \)/dL. If there is active lead exposure, other children and family members should be tested, especially young children and pregnant mothers. The half-life of lead in the blood is 28 to 36 days, so that low BLLs do not preclude prior exposure.12

Context of Lead Exposure
As per the preceding discussion, lead exposure often co-occurs with other risk factors, many of which are effect modifiers. Additional information should be obtained on stress, environmental deprivation or enrichment, including language and play, and nutrition, as well as exposure to other common toxins, including intrauterine alcohol and nicotine or secondhand smoke. Maternal health and mental health should be included as routine aspects of child assessment.62,63

Clinical Response
Children with BLLs \( \geq 10 \mu \text{g} \)/dL should be referred to a pediatrician for medical observation and follow-up. As per the CDC, chelation is indicated only for levels \( \geq 45 \mu \text{g} \)/dL. For children with levels <10 \( \mu \text{g} \)/dL, more general guidelines apply, including education on removing potential exposures and preventing exposure.38 Active enrichment should emphasize opportunities for learning and creativity, increased positive verbal interactions with caregivers, and other steps to promote language development.37

Nutrition
As noted above, studies show that children with diets deficient in calcium, folate, thiamine, iron, zinc, and vitamin C tend to be more strongly affected by lead toxicity. Iron supplementation (4–6 mg/kg/d) is recommended for children with lead poisoning and iron-deficiency anemia. Clinicians can recommend sensible diets that include all of these important nutrients.38 Current experimental evidence indicates that vitamin E (seeds, nuts and their oils, and many leafy green vegetables), beta-carotene (spinach, collards, and yellow and orange vegetables) and lipoic acid (liver, spinach, and broccoli) are also protective against oxidative damage, and can be safely ingested as part of a healthy diet.43,64

Conclusion
As developmental disorders increase, so do psychiatric referrals. Estimates of psychiatric disability in this population are as high as 50%.65,66 Mental health clinicians serving poor families with limited access to integrated services can play an important role in treatment by recognizing the role common toxins and psychosocial stress may have in patient disorders. Using the bioecological model, psychiatrists, primary care physicians, and mental health clinicians can recognize how environmental and constitutional factors interact, and can help develop comprehensive treatment approaches.

Acknowledgments
This article was supported in part by the cooperative agreement number U1U61TS000118-01 from the Agency for Toxic Disease Registry (ATSDR). Its contents are the responsibility of the authors and do not necessarily represent the official views of ATSDR. The US Environmental Protection Agency (EPA) supports the Pediatric Environmental Health Specialty Units (PEHSU) by providing funds to ATSDR under inter-agency agreement number DW-75-92301301-0. Neither the EPA nor ATSDR endorse the purchase of any commercial products or services mentioned in PEHSU publications.

Conflict of Interest Statement
Mary G. Burke, MD and Mark D. Miller, MD, MPH disclose no conflicts of interest.

References