ELSEVIER
SAUNDERS

Psychiatr Clin N Am
27 (2004) 745–753

PSYCHIATRIC
CLINICS
OF NORTH AMERICA

Occupational exposure and addictions for physicians: case studies and theoretical implications

Mark S. Gold, MD*, Joanne A. Byars, MS3, Kimberly Frost-Pineda, MPH

University of Florida College of Medicine, Gainesville, FL, USA

Risk of addiction through occupational exposure to drugs of abuse is an important public health problem that has received relatively little attention in the literature. Studies that do compare risk by occupation often point to stress and easy access as major explanations for increased substance use in certain populations. The most recent studies, however, using state of the art technology, are suggesting an alternate hypothesis. Increased risk of addiction in certain occupational settings may be related to exposures in the workplace that sensitize the reward pathways in the brain and promote substance use. Further studies of the relationship between exposure in the workplace and addiction are necessary.

Occupational exposure and addiction

Numerous studies have demonstrated higher rates of alcohol use disorders in bartenders, waiters, and waitresses as compared with the general public, measured both by direct assessment using *Diagnostic and Statistical Manual of Mental Disorders* criteria and indirect markers such as cirrhosis deaths [1–4]. The increased prevalence of alcohol use disorders in these workers, who have ready access to alcohol, suggests two possible hypotheses: that these occupations attract individuals who drink heavily, or that some aspect of working at these jobs increases the risk of problematic alcohol use. Although some evidence indicates that beverage servers choose their occupations based in part on the easy availability of alcohol [5], other

* Corresponding author. University of Florida Brain Institute, Post Office Box 100183, Gainesville, FL 32610-0183, USA.
E-mail address: msgold@psychiatry.ufl.edu (M.S. Gold).

doi:10.1016/j.psc.2004.07.006

data suggest that something about the job itself leads to increased rates of alcohol abuse and dependence. Unlike in other occupations associated with heavy drinking, such as construction work, unemployed beverage servers have significantly lower rates of alcohol dependence than those currently working in the industry [4].

Further support for the occupational exposure theory comes from a comparison of at-risk drinking in beginning students in the hotel and restaurant industry and students in other fields. After adjusting for age, the two groups did not show different patterns of alcohol consumption, suggesting that the increased prevalence of problem drinking in beverage servers derives from the nature of the employment rather than from self-selection [6].

Workers exposed to organic solvents also show elevated rates of problematic alcohol use. Studies of workers in otherwise similar occupations that differ in solvent exposure have found higher rates of at-risk drinking in the solvent-exposed groups. For instance, seamen working on chemical tankers appear to have a higher lifetime prevalence of heavy alcohol use and alcohol-related problems than seamen working in other fields; however, both groups reported similar past-year alcohol consumption [7]. Based on available data, it is difficult to say whether the increased prevalence in solvent-exposed workers is because heavy drinkers choose these industries, or because the hazardous and stressful nature of the work leads employees to seek out the anxiolytic properties of alcohol, or if exposure to toxic volatile solvents, many with central nervous system (CNS) effects, may play a role.

Are physicians, especially anesthesiologists, at increased risk?

Until recently, most doctors believed that addiction was a moral problem, a failure of will, or a disorder exclusive to those with mental disorders, a belief that may have caused many to fail to recognize their own risk of becoming addicted to the substances they used, with tragic consequences. Many physicians who played crucial roles in shaping modern medicine, however, also suffered from substance use disorders. Particularly in anesthesiology, some of the greatest pioneers in the field fell victim to addiction, as they became dependent on the drugs with which they worked.

Even in the early days of modern medicine, astute physicians fought to make their colleagues aware that anyone could be vulnerable to addiction. Writing in 1894, the medical director of the Brooklyn Home for Habitues argued that "it is easy to moralize on the weak will—as many, mistakenly, are wont to put it—of our hapless brother living under this blight, but talk about 'weak will' as a reason why strong men succumb to morphia [...] is twaddle" [8]. He warns against self-experimentation and implores any physician who thinks himself invulnerable to "not be blinded by an underestimate of the poppy's power to ensnare. Let him not be deluded by an overconfidence in his own strength to resist; for along this line history has

repeated itself with sorrowful frequency and—as my experience will well attest—on these two treacherous rocks hundreds of promising lives have gone awreck'' [8].

Modern inhalational anesthesia began as an offshoot of recreational drug use. The doctor credited with first using ether during surgery, Crawford Long, came up with the idea after noticing that the injuries he received in intoxicated falls at ether parties did not produce pain until after the drug had worn off [9]. Although not all early anesthesiologists used anesthetic gases for entertainment purposes, many extensively self-administered these drugs in the course of their research [10]. With a history that begins like this, it is apparent that addiction could qualify as an occupational hazard for anesthesiologists.

Perhaps the most famous physician to become addicted as a result of his work in anesthesiology is William Steward Halsted, whose contributions revolutionized surgery and medical education. His efforts to improve the practice of surgery led him to search for new and better anesthetic techniques. Realizing that cocaine had potential for use as regional anesthesia, Halsted, his friend and fellow surgeon Richard Hall, and their students began to self-experiment with the drug, injecting it into their nerves [11]. These investigations led to the development of the nerve block; unfortunately, they also led to the development of cocaine addiction in Halsted and his colleagues. Halsted's attempts to treat his condition led him to substitute a morphine addiction for the cocaine addiction; he remained drug-dependent for most, if not all, of his life [11]. His coinvestigators fared no better; in a letter to his friend William Osler, Halsted wrote, ''Poor Hall and two other assistants of mine acquired the cocaine habit in the course of our experiments on ourselves—injecting nerves. They all died without recovering from the habit'' [11].

A striking example of addiction resulting from occupational exposure to anesthesia may be the case of Robert Glover, the British physician who elucidated the pharmacologic and anesthetic properties of chloroform in a series of groundbreaking experiments in the 1840s [12]. Among his many other observations, Glover noted that he could detect the odor of chloroform on the breath of the dogs to which he had administered the drug intravenously [12]. Years later, while serving in the Crimean War, Glover contracted dysentery and was treated with opium and chloroform; he became addicted and died of a chloroform overdose in 1859 [12]. One can only speculate as to whether Glover's exposure to exhaled chloroform in the course of his experiments may have sensitized him to the drug and set the stage for his later dependence.

Addicted anesthesiologists

Case A is a 65-year-old retired military anesthesiologist who had a highly respected career. Case A smoked cigarettes until age 50 but had no other

family or personal history of substance use or addiction before sufentanil. Case A first used sufentanil intranasally at age 44, quickly progressing to up to 20 mL (1000 μg) per day. Case A never injected but would use fentanyl or morphine intranasally when he could not obtain sufentanil. After 2 years of drug use Case A's partners intervened, and Case A was treated for 5 months at a center that specializes in chemically dependent physicians. Case A entered a state's physician recovery program with a 5-year contract that he completed successfully, and Case A has been in recovery for over 10 years.

Case B is a 45-year-old anesthesiologist. Case B does not have a family history for addiction but did experiment with marijuana in college. Case B did not smoke, but did drink occasionally, usually enjoying fine wine. Case B had graduated from public high school and a state university with honors. After graduating from medical school, Case B entered a very competitive anesthesiology training program and was among the top residents. Case B married and had children and was very active in their lives. After residency, Case B became part of a major anesthesiology group. After 10 years in practice, Case B tried sufentanil intranasally, and within 3 days was injecting up to 30 mL (1500 μg) daily. Case B would awaken at 3 a.m. daily in withdrawal and inject to go to work. After more than 6 months of daily use, Case B overdosed in the operating room after injecting the drug and thereafter was admitted to a center with a tract for chemically dependent professionals for 3 months. Case B was monitored by a state physician health program, and has successfully finished a 5-year contract with clean urines and full compliance. Case B has been in recovery more than 5 years and is practicing addiction medicine.

Case C is a 48-year-old fellowship-trained cardiac anesthesiologist. Case C has been married twice and has children from both marriages. Case C graduated at the top of the class from high school and completed college 3 years later. Case C considered thoracic surgery before completing an anesthesiology residency at a major university medical center and completed a highly competitive cardiac anesthesiology fellowship. Case C does not have a family history of addiction. Case C never smoked tobacco, had tried marijuana for the first time while in medical school, and drank socially. At age 29, Case C briefly experimented with sublingual fentanyl during residency but did not use during the fellowship. At age 31, after entering private practice, Case C began to use sufentanil sublingually, up to 30 mL (1500 μg) daily, but did not inject. After 9 years of use, the chief of staff and the chief executive officer of the hospital intervened. Case C was treated at a center that specializes in chemically dependent physicians for 4 months and successfully completed a 5-year aftercare and monitoring program with a state physician health agency.

Certain similarities exist in the cases described. All were high-achieving students with no family history of addiction. They did not use drugs other than cigarettes (Case A), some marijuana experimentation in college and occasional social alcohol use (Cases B and C.). All three of these

anesthesiologists began abusing drugs to which they had access in the workplace. But was access what caused them to use sufentanil, or was it used in attempt to alleviate the withdrawal they felt when they were away from the exposure? The authors have heard first-hand accounts of anesthesiologists volunteering for extra call and long procedures, refusing breaks and staying after hours, and even that they experience withdrawal-like depression while on family vacations. If the brain is sensitized through repeated exposure, it is understandable how dependence results so rapidly when they begin to divert it for personal use.

Neurobiology of exposure

Exposure to powerful opiate drugs in the operating room can be expected, on the basis of the recent animal literature, to change the brain, motivation, and behavior. Robinson and Berridge have suggested that drug cues trigger excessive incentive motivation for drugs based on basic data showing that addictive drugs change brain activity and reward hierarchies in the nucleus accumbens and related systems [13]. In addicts, doses of drugs that are too low to produce any conscious recognition that they received drugs are still quite capable of inducing changes in the brain and influencing behavior, which would make it more likely that drugs are received [14]. The presence of drug-related cues or low doses of drugs also can trigger a drive for the drug in recovering addicts and those early in the abuse–addiction cycle. Animals need not self-administer potent drugs of abuse for sensitization to occur. In fact simply putting the drug into the nucleus accumbens by microinjection sensitizes the animal to further drug exposure or even wanting of sugar [15]. Sensitized neurons can be triggered by low doses of the drug (environmental opiate exposure), drug cues (seeing the operating room for a recovering anesthesiologist) learned to be associated with drug administration, or the chronic state where the physicians have been exposed to the point that they seek out opportunities to be in the operating room because of pathological, but not consciously recognized wanting of the drug.

Second-hand exposure may be the greatest for the physician at the patient's mouth but still this would result in low-dose exposure. For fentanyl, however, the potency of the drug is so great that even very small amounts would be expected to produce changes in the brain [16]. Some analogs are up to 1000 times as potent as heroin. Usually it is considered 200 times as potent as morphine with a prompt onset of action, less than 1 minute, and short duration of action, about 40 minutes. This makes it very much like cocaine, in that it is acutely reinforcing, has a rapid decay, and has a craving/anhedonia curve.

Dose may be important for overdose, but it is not critical for changing the brain. Low doses of opiate drugs can induce sensitization. The opposite of tolerance, sensitization makes drugs more and more compelling over

time. As drug use or drug exposure continues, the meso-telecephalic dopamine systems become reorganized to respond to drug cues and drugs themselves with vigor. Dopamine D1 receptors in the nucleus accumbens become hyper-responsive to drugs of abuse, promoting dopamine signal flow and possibly underlying sensitization. Glutamate, also released in the nucleus accumbens, appears to be sensitized by drug exposure [17]. In fact, most every brain system studied has been shown to be sensitized in the nucleus accumbens and related brain systems [18]. Caster and Goldman-Rakic [19] have shown that psychomotor sensitization can persist for years after drug exposure is discontinued. Sensitization is associated with long-lasting changes in the actual cell structure, length of dendrites, and extent of dendritic branching in the nucleus accumbens and prefrontal cortex [20]. Susceptibility to sensitization is a new area of investigation, but it is already clear that it is modified by genes, gender, stress, exposure to trauma, and prior drug experiences. Sensitization, however, is accompanied by reprogramming of the brain's reward systems [17,21]. When morphine is given to rats in a novel environment rather than the home, it causes more changes in the brain and more sensitization [22]. Expression of immediate early genes—including c-fos—by neurons is intensified by drug administration in novel environments [23]. Exposure, even low doses in the operating room of fentanyl or other potent drugs of abuse, can be assumed to change the brain and the person.

Drug-using anesthesiologists defy logic and call in to question logical thinking. Certainly, anesthesiologists understand that drugs of abuse are addicting and dangerous, but the sensitized brain is less rational. Drug-seeking and drug-related behavior can occur without conscious craving or conscious drive for the drug [24]. The cortex may serve as a rational and logical brake on drug taking, but the decision-making processes are compromised easily by emotions and acquired drug bias and denial. Many addicts share important neuropsychological deficits with patients with frontal and prefrontal lesions. Rogers [25] showed that opiate users have deficits in deciding between choices similar to patients with lesions of the orbital frontal cortex. Such a loss of cortical inhibition may increase the sensitization that accompanies addiction by removing the normal check and balance system.

After a drug or alcohol problem develops for anesthesiologist, decision-making is deficient. They overdose on nitrous in the on-call room; they overdose in the operating room itself; they inject themselves using unsterile precautions and in environments that they would never inject a patient. They steal the patient's drugs, inject and smoke patches, and put themselves at great risk for overdose and suicide. After treatment, anesthesiologists are noteworthy for being unable to return to the operating room. Some, even in simulator exposure, have gag reflex, panic, sweats, and flight. This may be explained by sensitization. Sensitization is a prime model for drug addiction relapse, as one dose of a drug reinstates the full syndrome of drug seeking

and drug use after long-term extinction [26]. Until better understood, anesthesiologists should consider change of career or specialty.

Although exposure may be greatest at the patient's mouth, where the anesthesiologist can be found, other factors also may explain their high rate of addiction. Exposure effects are magnified by stress. Anesthesiologists are the canary in the mine and the executive monkey at the same time. They are under continual stress and blamed at times when they actually have no control of the patient's status. Cross-sensitization has been reported in animals, so that drugs and extreme stress may inter-relate. Animals exposed to stress may become sensitized to morphine or cocaine, and animals sensitized by drugs become hyper-responsive to stress. Anesthesiologists may be particularly vulnerable because of the narcotic exposure and prior exposure to stress, inescapable stress, in the operating room.

To test this hypothesis, the authors recently developed new methods to detect propofol and fentanyl in the operating room [27]. First, they found that propofol, an intravenous anesthetic, could be detected in exhaled breath of volunteers. To sample environmental air in the operating room, the authors then designed a sensitive LC-MS-MS assay for fentanyl. They were able to detect fentanyl and propofol repeatedly (Figs. 1, 2) in the air of the operating room. In fact, the authors now can detect fentanyl reliably in the operating room atmosphere to 100 pg/mL and have found levels in excess of 100 pg/mL in the effluent from multiple medical gas monitors and the cardiopulmonary bypass machine [28]. They have measured fentanyl in every location in which they have tested. Additional studies to further measure exposure are underway.

Summary

Risk of addiction through occupational exposure to drugs of abuse is an important but relatively neglected public health problem. Stress and access may have much less of a role in addiction among certain populations than originally was thought. Risk of addition may be increased dramatically by unintentional exposure in the workplace to potent substances that sensitize

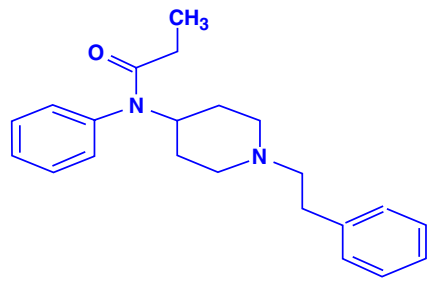

Fig. 1. Fentanyl.

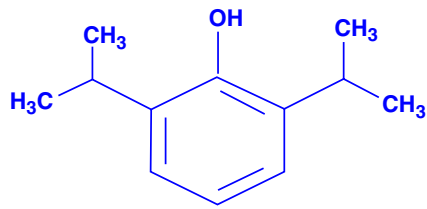

Fig. 2. Propofol.

the brain. Everyone knows that second-hand inhalation of crack vapors is a very dangerous proposition, but rarely has alarm been raised about exposing anesthesiologists to second-hand fentanyl. Additional studies of the relationship between exposure in the workplace and addiction are necessary. These studies should include biological measures, such as blood levels in exposed workers, and sensitive assays that quantitatively assess levels of exposure in the workplace.

References

[1] Leigh JP, Jiang WY. Liver cirrhosis deaths within occupations and industries in the California occupational mortality study. Addiction 1993;88(6):767–79.
[2] Dimich-Ward H, Gallagher RP, Spinelli JJ, Threlfall WJ, Band PR. Occupational mortality among bartenders and waiters. Can J Public Health 1988;79(3):194–7.
[3] Harford TC, Brooks SD. Cirrhosis mortality and occupation. J Stud Alcohol 1992;53(5): 463–8.
[4] Mandell W, Eaton WW, Anthony JC, Garrison R. Alcoholism and occupations: a review and analysis of 104 occupations. Alcohol Clin Exp Res 1992;16(4):734–46.
[5] Nusbaumer MR, Reiling DM. Environmental influences on alcohol consumption practices of alcoholic beverage servers. Am J Drug Alcohol Abuse 2002;28(4):733–42.
[6] Larsen S, Jorgensen H. Better than their reputation—do hotel and restaurant students drink more? Food Service Technology 2003;3:151–5.
[7] Moen BE, Sandberg S, Riise T. Drinking habits and laboratory tests in seamen with and without chemical exposure. J Stud Alcohol 1992;53(4):364–8.
[8] Mattison JB. Morphinism in medical men. JAMA 1894;23:186–8.
[9] Long CW. An account of the first use of sulfuric ether by inhalation as an anaesthetic in surgical operations. In: Nuland SB, editor. The origins of anesthesia. Birmingham, AL: Classics of Medicine Library; 1983. p. 705–13. Taken from: Southern Medical and Surgical Journal 1849;5(12):705–3.
[10] Defalque RJ, Wright AJ. Early French accounts of self-inhalation of ether and conscious analgesia. Anesthesiology 1995;86(3):1370–1.
[11] Penfield W. Halsted of Johns Hopkins. JAMA 1969;210(12):2214–8.
[12] Defalque RJ, Wright AJ. The short, tragic life of Robert M Glover. Anaesthesia 2004; 59(4):394–400.
[13] Robinson TE, Berridge KC. Addiction. Annu Rev Psychol 2003;54:25–53.
[14] Fischman MW, Foltin RW. Self-administration of cocaine by humans: a laboratory perspective. CIBA Found Symp 1992;166:165–80.
[15] Wyvell CL, Berridge KC. Incentive sensitization by previous amphetamine exposure: increased cue-triggered wanting for sucrose reward. J Neurosci 2001;21:7831–40.

[16] Henderson GL. Designer drugs: past history and future prospects. J Forensic Sci 1988;33: 569–75.
[17] Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2001;2:695–703.
[18] Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive–sensitization view. Addiction 2000;95:S91–117.
[19] Caster SA, Godlman-Rakic PS. Long lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys. Neuropsychopharmacology 1999;20: 10–28.
[20] Robinson TE, Kolb B. Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. Synapse 1999;33:60–2.
[21] Everitt BJ, Wolff ME. Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 2002;22:3312–20.
[22] Badiani A, Oates MM, Robinson TE. Modulation of morphine sensitization in the rat by contextual stimuli. Psychopharmacology 2000;151:272–82.
[23] Klebaur JE, Ostrander MM, Norton CS, Watson SJ, Akil H, Robinson TE. The ability of amphetamine to evoke arc mRNA expression in the caudate, nucleus accumbens and neocortex is modulated by environmental context. Brain Res 2002;930:30–6.
[24] Elster J. Strong feelings: emotion, addiction, and human behavior. Cambridge (MA): MIT Press; 1999.
[25] Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers. Neuropsychopharmacology 1999;20:322–39.
[26] De Vries TJ, Shippenberg TS. Neuronal systems underlying opiate addiction. J Neurosci 2002;22:3321–5.
[27] Gold MS, Frost-Pineda K, Pomm R, Melker RJ. Is addiction an occupational hazard for anesthesiologists? Philadelphia, PA: The College on Problems of Drug Dependence, 2004. Available at http://biopsych.com:81/cpdd_web/
[28] Gold MS, Melker RJ, Pomm R, Frost-Pineda K, Morey T, Dennis DM. Anesthesiologists *are* exposed to fentanyl in the operating room: addiction may be due to sensitization. International Journal of Neuropsychopharmacology 2004;7(S1):p01.023.