Chronic Toxicity of Cocaine use

Once the patient survived the symptoms of an overdose, what can they look forward to next ? Cocaine, even for those who feel that they don't use that much or that often, has some chronic effects that are not to be scoffed at. Paranoia is a consequence of alterations in dopamine activity, particularly in the limbic system. It is well known that other CNS stimulants (amphetamines, methylphenidate, etc.) can cause psychotic manifestations. Cocaine taken over some time, and in varying amounts, can lead to behavioral abnormalities, which manifest themselves most frequently as suspiciousness, hostility, delusions, hallucinations, etc. For example, many "regular" users of cocaine carry firearms, which can lead to visits to the emergency room (ER) secondary to shot wounds acquired in violent attacks.

An especially bizarre effect of cocaine are the so-called "Coke Bugs", altered tactile sensation (tactile hallucination) that bugs are crawling under one's skin (Fig. 45). This can lead to a person actually picking imaginary bugs off their arms and legs with tweezers and such (self excoriation). It is recorded that individuals suffering from this hallucination have produced *proof* of the existence of the "*bugs"* by bringing little vials of them into the ER of course when examined the "bugs" turn out to be pieces of dead skin.

Much more commonly, chronic users of cocaine are unaware of the long-term damage being done to their bodily part. A prime example is the recent finding in animal studies of cardiac enzyme depletion. While not adequately evaluated in humans yet, the consequences may be that younger users are setting themselves up for serious cardiac compromise in the future. Some pathologists at Stanford looked at autopsy findings of persons who had died of cocaine-associated sudden death. Their findings were startling as they discovered that cocaine users demonstrated *wide-spread, intense, contraction band necrosis*, and they felt that death resulted when this necrosis supplied the *anatomic substrate for a malignant type re-entry arrhythmia* [50, 51].

Once the recreational user turns into a chronic user, brain lesions in PET studies are demonstrated. This is accompanied by abnormalities in the dopaminergic system with an increased release in the metabolite homovanillic acid (HVA), which is accompanied by symptoms of Parkinson and tremor suggesting a deficit in the transmitter dopamine [52].

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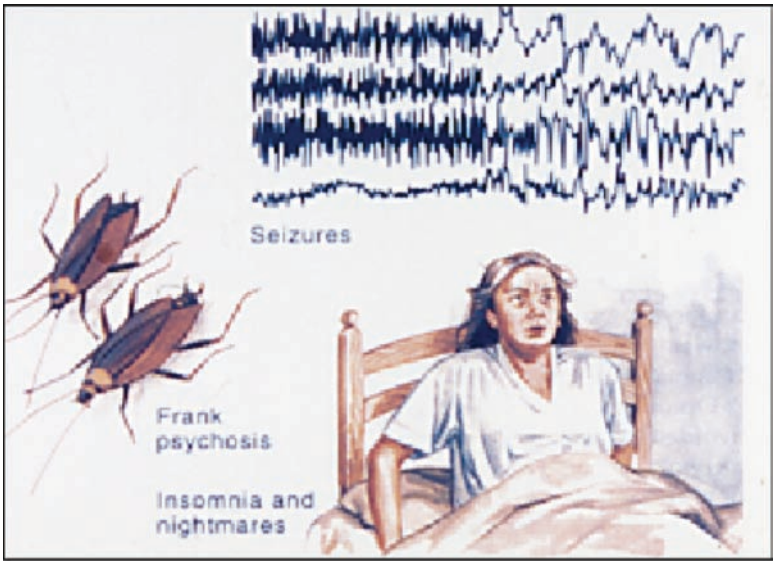

Fig. 45 Effects of chronic abuse of cocaine with seizures, tactile paranoia, visual hallucinations and insomnia

The entry of cocaine molecules into the system causes an abnormal increase of neurotransmitters at the synapse, leading to an overstimulation of the reward areas and a feeling of intense euphoria. This state may be accompanied by paranoia and hyperexcitability. With continued use, cocaine molecules further interfere with the release of neurotransmitters and block the receptor sites in the reward area. At the same time, the number of receptor sites increases, resulting in an even greater discrepancy between the amount of transmitter available and the number of receptor sites occupied (Fig. 46). Since cocaine also works by stimulating the release of neurotransmitters, and they are now short in supply, more cocaine is required to obtain a *high*. Craving remains at a high level, and the user experiences a generalized feeling of depression and unhappiness. Eventually, these symptoms become severe and terminate in the *crash*, which is characterized by intense craving, insomnia, restlessness, and anhedonia (profound depression, total absence of pleasure, and increased feelings of worthlessness).

Lastly, problems with the nasal passages are common, sometimes ‘requiring surgery for repair of perforated septa, and finally, for the IV users, there is the potential of acquiring AIDS.

A rather interesting and not fully understood effect of repeated cocaine use is called *kindling*.’ This refers to a phenomenon of *reverse tolerance* that has been seen in the laboratory, but not yet confirmed in humans [53]. It seems that repetitive, subthreshold electrical stimulation of the limbic system, which relied on dopamine as a neurotransmitter, can lead to sensitivity to catecholamines, and lower the

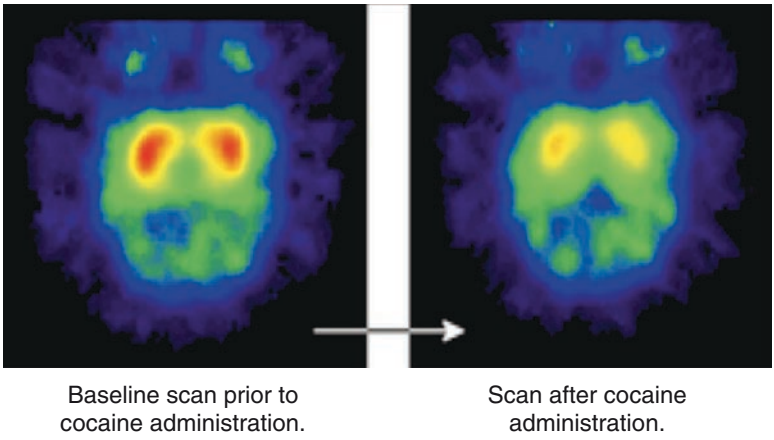

Fig. 46 Positron Emission Tomography (PET) scans showing the average level of dopamine receptors in primates' brains. Red is high- and blue is low-concentration of dopamine receptors. The higher the level of dopamine, the fewer receptors there are. This chronic use results in an increase of receptors, however, with less dopamine being available for binding

seizure threshold. This may help to explain why the next dose, even if it is less than that usually taken, might be the one that kills the user. In this respect it is hypothesized that carbamazepine (CBZ), which is an anticonvulsant medication has a potential as a treatment for cocaine abuse because of its ability to block cocaine-induced "kindling" in rodents [54]. Since kindling has also been postulated to be a model for the neurophysiological basis of cocaine craving, CBZ may reverse the DA receptor supersensitivity that purportedly is the result from chronic cocaine use, and its potential as a treatment for cocaine dependence.