Withdrawal syndromes

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Substance abuse has become a common problem in our society, but there is a limited amount of information conveniently gathered together for guidance in medical practice in relation to withdrawal syndromes. Here an attempt is made to do so for the major items which are abused.

Alcohol

The exact mechanisms involved in the appearance of withdrawal symptoms await clarification. However, at a biochemical level, the proposals, argued for by Littleton[1], that regular intake of alcohol causes cellular adaptation increasing cellular activity on withdrawal, are convincing. If it is also the case that cell membranes can be permanently altered, then this may offer an explanation for clinically observed persistent potential for symptoms after a long period of abstinence and the rapid reinstatement of dependence. However, psychological explanations complicate this issue.

The manifestation of withdrawal symptoms does not require total abstinence; a fall in the blood alcohol concentration of 100 mg per 100 ml from whatever level will precipitate a withdrawal syndrome[2]. It is thought that the most severe withdrawals occur when a binge is superimposed upon a high baseline level of consumption, and it is for this reason that, contrary to popular belief, the vagrant population, which cannot financially sustain a high basic level, does not experience severe problems on detoxification [3]. The global nature of cerebral dysfunction during withdrawals has been reported [4]; cerebral blood flow decreases by 19 per cent during the first two days. The reduction in flow correlated with length of the previous drinking bout but there were highly significant regional variations associated with symptoms.

The severity of symptoms depends to a considerable extent on the amount and duration of alcohol consumption. The most common withdrawal symptom (tremulous state) begins within the first 24 hours after ceasing or reducing the intake. Hershon [5] has, however, drawn attention to the wide range of symptoms attributed to withdrawal. He differentiated between those symptoms which occur most commonly during withdrawals (though not necessarily part of withdrawal), such as depression, anxiety, tiredness, and craving, and those symptoms that are more specific to withdrawal, such as shaking of the body and hands, panicking, inability to face the day, and guilt.

A recent quantitative study of 43 alcoholic inpatients found that total alcohol intake (and total intake/body weight) over the preceding seven days correlated significantly with severity of acute withdrawal, while duration of heavy drinking did not [6].

Disturbance of sleep is accompanied by an increase in rapid eye movement (REM) sleep and vivid dreams with hypnagogic and hypnopompic hallucinations. These all tend to disappear within 48 hours. In the more severe cases, a second stage can develop after two or three days. This involves disorientation, visual and auditory hallucinations, seizures and delirium tremens (DTs). Less than 5 per cent of patients with withdrawal symptoms will develop delirium tremens [7].

Edwards [8] has described a transient hallucinatory state which may be auditory, such as hearing someone call, or visual, such as seeing a rat move across the floor.

Withdrawal seizures, usually in runs of 3–4 but sometimes separately, occur in 5–15 per cent of the cases [7,9,10] within 12–36 hours of reduced intake. The risk of seizures is greatly increased in cases of polydrug abuse. The hallucinatory phenomena are thought to be continuous with alcoholic delirium and about one third of the patients who experience seizures develop this serious condition. Any history suggestive of the onset of DTs is an indication for hospitalisation.

The alcoholic withdrawal syndrome is self-limiting, usually with complete recovery. One after the other different pharmacological approaches have been proposed, such as phenothiazines, paraldehyde, butyrophenones, benzodiazepines, propranolol, chlormethiazole (Heminevrin) etc. The major tranquillisers have the serious disadvantage of being potentially epileptogenic, so they should be avoided when there is no precise indication [11,12] for their use.

Most of the literature suggests strongly that benzodiazepines are on the whole far better than paraldehyde [13].

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Among benzodiazepines, chlordiazepoxide is preferred by most clinicians but some feel that clobazam is more effective because of its longer half-life ($t\frac{1}{2}$ = 18h) [14].

Propranolol has been used with other drugs to decrease peripheral autonomic overactivity, thus stopping a negative feedback of anxiety [15,16]. Heminevrin has been widely used but its prescription requires caution because of its addictive properties [17,18,19]. The preventive prescription of anticonvulsant drugs, such as diphenylhidantoin has always been controversial [10,11]. With rare exceptions, intravenous fluids should not be used since the typical alcoholic going through withdrawal is overhydrated[20].

Finally, one must keep in mind the pathological conditions that are usually present in chronic alcoholic persons. These include cardiovascular disease, liver disease, gastrointestinal disturbances and muscular and nervous problems [7,21,25].

It appears fairly well established that the type of treatment given for acute withdrawal (ie sedative medication vs. social detoxification) has little influence on short-term outcome for most patients; little else in this field is well established [26].

Opiates

Opiates are pharmacological substances similar to morphine, and include natural alkaloids of opium (morphine, codeine, papaverine, thebaine), semi-synthetic products such as heroin, desmorphine, dihydromorphine and dihydrocodeine, and the synthetic products like pethidine, dextromoramide, dextropropoxiphene, methadone and norpethidine.

The opiate withdrawal syndrome is, after the alcoholic withdrawal syndrome, one of the most widely known and better described. Compared with the withdrawal from other substances (eg barbiturates), withdrawal from opiates is not so life-threatening [27].

The most common type of withdrawal is a mixture of emotional, behavioural and pathological symptoms [28]. The severity of the symptoms depends on the kind of substance, on the amount and duration of use, on the general physiological condition of the user, and on the psychological factors involved. The onset and duration also vary, depending on the substance [27]. From 6 to 12 hours after stopping heroin or morphine, symptoms appear, such as craving for the substance, anxiety, irritability, depression, yawning, sneezing, lacrimation, rhinorrhoea, salivation, sweating, shivering and gooseflesh. The pupils dilate, there are muscle cramps, anorexia, diarrhoea and vomiting. Body temperature and blood pressure may be slightly elevated and the effect on the pulse is variable. Incontinence of urine and spontaneous orgasm or ejaculation may also occur [11,12,29].

The symptoms of withdrawal peak at 2–3 days and have usually gone within 5–10 days if untreated. Tolerance to opioids substantially disappears with the end of the withdrawal syndrome [12,29].

Because of the long-lasting pharmacological action of methadone after abruptly stopping its use, withdrawal symptoms start after between 36 and 75 hours, and peak at around the 6th or 7th day, disappearing in 10 to 20 days[27]. Some authors suggest that mild symptoms could last for one to two months[12].

There is a big controversy in the literature regarding the severity of the methadone withdrawal syndrome compared with withdrawals from other opiates. One group holds the view that the symptoms are more gradually presented and less severe in the methadone withdrawal syndrome [30]. On the other hand, claims that these symptoms are more torturing [31] compared with the heroin withdrawal symptoms, especially in the newborn from a mother dependent on methadone [32]. An alternative view suggests that no withdrawal syndrome at all is then likely [33]. It is agreed that muscular cramps, autonomic overactivity, diarrhoea and vomiting are definitely milder in methadone withdrawal, but these symptoms last longer than those following other opiates [31].

The withdrawal symptoms of meperidine begin after three hours, peak between 8-12 hours and disappear in 3-5 days. Withdrawal syndromes also occur after the use of high doses of pentazocine and propoxyphene [34,36].

The most severe withdrawal symptoms from opiates appear in newborn children from opiate-dependent mothers. The onset depends on various factors: (a) time of the last dose before giving birth; (b) the amount of the substance; (c) other substances in the mother's blood at the same time; and (d) the infant's metabolic and excretion rhythms. The incidence of withdrawal symptoms in the newborn child is 50–91 per cent [37,38]. Usually the symptoms from heroin withdrawal start 24–48 hours after birth and from methadone within the first four days, but last longer. The symptoms extend from insomnia, fever, crying, respiratory disturbances, spasms, clonus and abrasions, to severe vomiting, dehydration, acidosis and death [27].

Methadone and heroin produce basically the same symptomatology in the newborn child but spasms are more frequent following methadone [32,37,38]. Spasms occurred in only eight of 384 babies born to heroin-dependent mothers and in five babies of 46 born to mothers dependent on methadone [38]. Mortality without treatment varies from 34–93 per cent [27].

It is important when treating a person with a withdrawal syndrome to know the exact dose of a substance used, but unfortunately this is not always possible due to the adulterations which may range from 0–75 per cent for heroin, but are usually between 3 and 5 per cent. The most common adulterative substances in the black market are lidocaine, procaine, quinine and lactose [39]. The average daily dose of heroin for an addict is 0.25–1 g, but there are some addicts who have used five grams a day [12].

The most common treatment for opiate withdrawal symptoms is methadone, because it blocks the symptoms without inducing euphoria [30]. Many drugs like diazepam, chlorpromazine, propranolol, and chlordiazepoxide, have been used [40]. As a general principle, the initial dose of methadone is 10–20 mg by mouth every two to six hours until the symptoms are controlled. The usual daily dose is 80–120 mg; some believe the initial dose must be continued for two to three days and gradually decreased.

The timing of decreasing methadone dosage varies from one therapeutic centre to another. For patients with a severe withdrawal syndrome and addicted to high doses of opiates it has been recommended that the decrease is at a rate of 20 per cent daily [30]. For mild syndromes (40 mg stabilising doses) the dose can be reduced from between 5-10 mg daily without problems [41]. For a withdrawal syndrome in a newborn child several alternatives have been proposed but the topic is out of the scope of this article [see however 32,37,38].

Kleber [42] reported that psychological factors play a major role in the opiate withdrawal syndrome. In particular, he showed that the personality factor of neuroticism and the addict's expectations about withdrawal are strongly related to the maximum level of withdrawal distress subsequently experienced during detoxification. He suggested that duration of use may be related to withdrawal severity only up to a certain point, and that after two or three months it has little effect.

Stitzer *et al.* [43] found that knowledge about the dose reduction schedule served to reduce complaints and they suggested that much of the withdrawal symptoms may be a result of anxiety and uncertainty.

The main clinical implication of these results is that attention should be paid to the psychological state of the addict before and during the process of drug withdrawal. Phillips *et al.* [44] found that, when withdrawing addicts from opiates, providing the individual with information about the sort of intensity of symptoms that might occur, could reduce withdrawal distress. Our own experience suggests that four days is in fact enough to reduce almost all opiate abusers' supplies to nil, without significant hardship.

Benzodiazepines

It is generally accepted that benzodiazepines in the ordinary prescribed doses can produce psychological and physical dependence [45–52].

Because of the high tolerance of these substances people can increase the daily dose up to a level of 80–150 mg of diazepam, or equivalent dose of other benzodiazepines.

There are mainly two kinds of abusers; one is a group of middle-aged people who have been introduced to the drugs through therapeutic prescribing, and the second are younger people who use these substances within the framework of drug addiction [53-56]. Dependent individuals prefer benzodiazepines which are rapidly absorbed and readily cross the blood-brain barrier, such as flunitrazepam [57].

Authors seem to agree that a therapeutic dose taken for 10–16 weeks and suddenly stopped can produce mild withdrawal symptoms [58], but it has been also suggested that 45 mg of diazepam or its equivalent for more than 8–10 weeks can produce symptoms similar to alcohol or barbiturate withdrawal syndromes, but with less severe autonomic overactivity [59].

Withdrawal symptoms depend on the kind of substance and on its amount and the duration of consumption [60]. The association of other substances, like alcohol or barbiturates, precipitates the appearance of withdrawal symptoms [61].

From 15 to 45 per cent of the long-term users of benzodiazepines can present a withdrawal syndrome [51,62,63]. The most common symptoms are anxiety, dysphoria, insomnia, concentration disturbances, panic reactions, sweating, palpitation, anorexia, headache, tremor, muscular spasm, metallic taste, depersonalisation and derealisation [45,49,52,64]. Some of the above symptoms are part of the anxiety state for which the benzodiazepines were prescribed. The anxiety state often reappears more severely if the benzodiazepines are stopped abruptly after four weeks, therefore the differential diagnosis between these two conditions is of great clinical importance [65-68].

More severe disturbances in the pattern of sleep seem to be produced by the shorter acting benzodiazepines [69]. The withdrawal symptoms are usually mild during the first two to three days, peak between the fifth and the ninth day, and decline within three to four weeks, though very mild states can last for even three months [12,27,68,70].

The presence of perceptual disturbances or the occurrence of seizures in a person who takes benzodiazepines should strongly suggest withdrawal. Delirium and epileptic seizures can occur in 5–20 per cent of the users of approximately 100 mg a day of diazepam or its equivalent dose of other benzodiazepines, within 3–5 days of abruptly stopping [45,61,71]. Most of these people who had epileptic seizures have been treated at an initial stage with major tranquillisers or antidepressants because of the nature of the withdrawal symptoms [72–75].

Three to four days after the benzodiazepine withdrawal is over, some individuals having previous histories of psychotic illness can again present psychotic symptoms or worsening of some of the existing ones. In such a case the benzodiazepine should be reinstated, controlling the symptoms in 24 to 48 hours [45,46,59,76].

Long-acting benzodiazepines, like diazepam and chlordiazepoxide, are to be preferred in the treatment of withdrawal symptoms. They must be given for 10 days and after that gradually reduced for at least four weeks [62,77,78].

As a general rule, when prescribing benzodiazepines for therapeutic purposes it is widely accepted that it is contraindicated to prescribe them for more than two months [79].

Stimulants

This group includes all the substances that stimulate the central nervous system (CNS) at different levels. The most representative are amphetamines, methylphenidate, cocaine and caffeine [80].

It is hotly debated whether these substances really produce withdrawal symptoms. Many authors do not agree with the giving of any pharmacological treatment in such cases [11,61]. Others suggest that the most severe symptoms are the persistent lethargy, sleep disturbances and depression. The lethargy lasts for 12–24 hours and the sleep disturbances, namely vivid dreams and in-

creased REM sleep, can last some weeks [12]. Depressive mood and very persisting suicidal ideas, which very often lead to suicide, must be treated with the patient in hospital [12,41,61,81-83]. Minor symptoms, such as weakness, hunger, apathy and muscular aches, can last beyond a month [61,66,81].

Because of the high and rapid tolerance to these substances [66,81], withdrawal symptoms can develop in individuals using the same dose for a given period.

From a physiological point of view the withdrawal syndrome is never lethal and recovers without treatment in 4–5 days [11], even though some clinicians suggest that major tranquillisers and gradually decreasing doses of the abused substances are indicated [84].

Cocaine

The chemical structure of cocaine is very similar to most local anaesthetics and its biological half-life is just one hour. In the CNS it produces stimulation like that following amphetamines; lately, its misuse has dramatically increased, especially in its new form called 'Crack'. Views on the withdrawal syndrome are controversial but craving for the substance is very high and the rest of the symptomatology is similar to that described for stimulants in general [85-87].

After alcohol, cannabis and its derivatives are the most widely abused substances. The active component is delta-9-tetrahydrocanabinol (THC). Once again, some authors reject the existence of any withdrawal symptom [11,61]. Others describe a mild withdrawal symptomatology with insomnia, irritability, anorexia and an increase of REM sleep, which goes in 4–5 days without any treatment [88]. THC is deposited in fat and then gradually released when the consumption has stopped; this allows a sort of gradual self-withdrawal of the substance, accounting for the minimal or non-existent withdrawal symptoms.

Barbiturates

Barbiturates were used in clinical practice for the first time in 1903, and their use reached a peak during the 1960s. As the knowledge of their addictive properties increased and safer products, like benzodiazepines, became available, prescribing and misuse also went down [89]. Some barbiturates, especially the short and medium acting ones, are still in use as anaesthetics and anti-epileptics [90].

As with the other drugs discussed, the barbiturate withdrawal syndrome depends on the kind of substance, degree of dependency, time of use and metabolism of the user. It is possible to have withdrawal symptoms even after a few weeks of use [66].

Individuals on large doses of short and medium-acting barbiturates risk developing very severe withdrawal symptoms from the first 24 hours after abruptly stopping. In cases of chronic abuse of approximately 800 mg of phenobarbital or secobarbital daily, abruptly stopping produces symptoms such as insomnia, severe autonomic over-reactions, psychological disturbances, and in a vast majority of cases, seizures and delirium. Fifty per cent present a condition very similar to alcoholic DTs. Hyperpyrexia, often appears in 36-72 hours and may last a week; it is often fatal if treatment is not started in three days from the last dose of barbiturates [41,61,91].

Three months on a daily dose of 400 mg of phenobarbital, or an equivalent dose of another barbiturate, produces in one-third of the users mild withdrawal symptoms and EEG disturbances. Abuse of 600 mg for one or two months produces in 50 per cent of the individuals a mild withdrawal syndrome, but 10 per cent present severe symptoms such as seizures. Finally, 900 mg a day for two months produces the same severe symptomatology in 75 per cent [66]. The treatment suggested is phenobarbital because of its long half-life (approximately four days). It provides a more constant serum level, and 30 mg of phenobarbital is recommended for each 100 mg of pentobarbital and equivalent. Stabilisation doses should be maintained for two days and then decreased by 30 mg each day [30,41,92].

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