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Drug Withdrawal Syndromes

A Literature Review

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Drug withdrawal syndromes reportedly have been caused by numerous pharmacological agents, but only a few drugs have been adequately studied in this regard. Criteria for evaluating drug withdrawal syndromes have been proposed. Sedative-hypnotic agents, opiates, corticosteroids, clonidine, tricyclic antidepressant medications and beta-adrenergic blocking agents meet the criteria for such syndromes. Gradual tapering of the dose of these drugs is recommended when therapy must be discontinued. Whether or not other drugs cause rebound reactions is questionable, but caution should be used when discontinuing drugs for which numerous reports of withdrawal syndromes exist.

DRUG WITHDRAWAL SYNDROMES are often mistaken for disease states in clinical practice. This article attempts to clarify the significance of some of these syndromes. The evaluation of drug withdrawal syndromes is difficult. Symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a "catching up" of the basic disease state, which may emerge in the absence of the pharmacological action of the drug. Symptoms not related to the underlying disease, such as those related to continued use of other drugs, may further cloud the issue. The simultaneous discontinuation of multiple drugs, addition of an interacting substance or questionable patient compliance all complicate determining the cause of these apparent drug withdrawal syndromes accurately. Also, psychological dependence may need to be distinguished from physiological withdrawal. For many drugs, only a few cases of withdrawal have been reported. The existence of true drug withdrawal must be shown by (1) a trial of gradual versus abrupt drug termination, (2) the appearance of symptoms more severe than baseline symptoms or (3) the onset of symptoms in newborn infants whose mothers have been taking the drug.

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Alcohol

The alcohol withdrawal syndrome is a manifestation of neuronal excitability. The syndrome is similar to withdrawal from other drugs in that the severity of symptoms depends on the size of the dose taken and the duration of consumption. The abstinence reactions occur in two phases. Minor symptoms such as insomnia, irritability and tremors usually appear within 24 hours of discontinuation, and disappear within 48 hours. A second, more serious phase develops after two to three days in severe cases of withdrawal. It includes hal-

lucinations, convulsions and delirium tremens (DT). Delirium tremens, however, occurs in less than 5 percent of patients in hospital who undergo withdrawal.[1] Rebound thrombocytosis appears during alcohol withdrawal in patients with either normal or depressed platelet counts at admission. Elevated counts begin 5 days after admission, peak between 10 to 15 days, with counts as high as 788,000 per cu mm, and last up to three weeks.[2,3] This was offered as a possible explanation for recurring venous thrombosis and pulmonary embolism in two of five patients.[3] Other causes of thrombocytosis were not evident.

Alcohol withdrawal has been treated with numerous pharmacological agents, primarily phenothiazines, paraldehyde and benzodiazepines. Phenothiazines have a distinct disadvantage in their inability to prevent seizures. Controlled trials and extensive clinical experience have shown the superiority of benzodiazepines over paraldehyde.[4] Thus, the benzodiazepines have emerged as the agents of choice for treating alcohol withdrawal. Among the benzodiazepines, chlordiazepoxide has been heralded as the most effective agent, but no controlled trial is available to support this theory.

Anticoagulant Drugs

As a result of retrospective studies, clinicians believed for many years that abrupt cessation of therapy with anticoagulant drugs caused an increased incidence of sudden deaths, myocardial infarctions and anginal attacks. *Rebound* hypercoagulability with resulting thromboembolism was thought to be the cause.[5] As a result, gradual withdrawal of anticoagulant agents was advocated for approximately 25 years. Recently, however, some practitioners have stopped oral warfarin therapy abruptly without increased prevalence of complications.

In a double-blind, prospective study of 78 patients with anginal symptoms and previous myocardial infarctions (MI's), there were no significant differences in the number of myocardial reinfarctions, thrombotic episodes or sudden deaths between the group of patients in whom phenindione was withdrawn abruptly and the group in whom the drug was withdrawn over six weeks.[6] Abrupt or gradual termination of phenindione therapy after two years carried a greater risk of complications than treatment continued for longer than two years. In two other studies of 134 patients with coronary artery disease, abrupt discontinuation of the drug did not carry a higher risk of thromboembolism than gradual tapering when measured by the prevalence of sudden deaths, deaths after acute MI's or increased symptoms of angina.[5,7] It appears that anticoagulant drugs given orally need not be tapered.

Anticonvulsant Drugs

Except for a few cases of status epilepticus resulting from abrupt withdrawal of phenobarbital, little proof exists of an anticonvulsant withdrawal effect in patients with epilepsy. However, barbiturate withdrawal has precipitated seizures in patients not previously predisposed to epileptic disorders. Documentation of status epilepticus from withdrawal of other anticonvulsant medications, including phenytoin and clonazepam, is lacking.[8] One uncontrolled investigation found that abrupt discontinuation of phenytoin did not precipitate convulsions.[8] Another symptom, acute psychosis, has been reported in two patients in whom anticonvulsant medication was gradually withdrawn.[9] The most conservative management plan suggests a gradual tapering of medication over nine months after four years without seizure activity.[10] Until definitive studies are done, caution should be taken to avoid abrupt discontinuation of anticonvulsant drugs in epileptic patients.

Antipsychotic Drugs

The abrupt cessation of antipsychotic drugs appears likely to induce withdrawal symptoms,[11] usually beginning one to two weeks after withdrawal. These include nausea, vomiting, diarrhea, headaches, perspiration, restlessness, insomnia, rhinorrhea, increased appetite and giddiness.[11-13] The occurrence of symptoms ranged among various clinical studies from 17 percent to 75 percent.[11] Withdrawal from phenothiazine therapy apparently does not induce convulsions.[12] Withdrawal symptoms are not dose or plasma level related.[12]

All antipsychotic medications have central and peripheral antimuscarinic properties. It has been proposed that withdrawal symptoms are due in part to an anticholinergic rebound reaction.[11-13] Agents with the most potent anticholinergic properties, such as chlorpromazine and thioridazine, are associated with the highest rate of withdrawal symptoms.[11,12]

Drug-induced Parkinson disease improves with withdrawal of the drug. However, parkinsonism may develop in a patient in whom an antiparkinson medication and an antipsychotic drug are

abruptly withdrawn simultaneously. The proposed mechanism for this phenomenon is that a temporary exacerbation of Parkinson disease results from an unopposed dopamine-blocking effect of the slowly excreted phenothiazine in the absence of the rapidly excreted antiparkinson drug. Typical symptoms include rigidity, tremors and akinesia. Usually these effects peak in approximately four days but can last for as long as four months.[12]

Withdrawal dyskinesia resembles tardive dyskinesia, but is self-limiting and appears for the first time following discontinuation of antipsychotic drug. Dyskinetic symptoms uniformly appear within a few days of termination of therapy, and may last for 1 to 22 weeks; however, they generally last for 6 to 12 weeks.[12] This condition probably results from a temporary hyperdopaminergic state in the basal ganglia following cessation of antipsychotic dopamine blockade.

Symptoms of anxiety or insomnia resulting from withdrawal of the antipsychotic drug are not easily differentiated from schizophrenic symptoms. Therefore, once the decision is made to withdraw antipsychotic medication, gradual tapering is suggested to reduce the possibility of somatic or extrapyramidal symptoms, as well as a relapse into a psychotic state.[11-13] If treatment with an anticholinergic agent is to be stopped, it should be discontinued several days after antipsychotic drugs are withdrawn. The only trial of abrupt or gradual withdrawal of antiparkinson medication showed that symptoms occurred more often and were more severe following abrupt discontinuation.[14]

Barbiturates

Withdrawal symptoms resulting from discontinued use of barbiturates are well known.[15] The likelihood of these symptoms developing depends on the degree of dependency on the drug before withdrawal, the duration of drug use and the rate at which the drug is metabolized. Patients who are physically dependent on large doses of short- or medium-acting barbiturates are at great risk of suffering major complications upon withdrawal.

Isbell stated that in all subjects who were taking more than 800 mg of pentobarbital or secobarbital daily, minor withdrawal symptoms developed upon discontinuing the drug. These include tremors, weakness, insomnia, sweating and restlessness. In 75 percent of patients taking this dose convulsions developed, and in 60 percent delirium tremens occurred upon withdrawal.[16] Except for rare instances, patients taking 600 mg or less per day of barbiturates exhibit only minor symptoms upon abrupt cessation of their use.

After abrupt withdrawal of the drug, there is a direct relationship between the severity of symptoms and when they begin.[15] Within 24 hours, tremors, weakness, insomnia, diaphoresis, restlessness, headache, malaise, nausea, vomiting, anorexia, dry mouth and deep tendon hyperreflexia may occur. Psychological features that are frequently encountered include apprehension, acute anxiety, irritability and depression.

If a patient has been taking barbiturates in large doses or for a long time, severe neurological symptoms may appear within 24 to 72 hours following their withdrawal. Myoclonic muscular contractions, spasmodic jerking of extremities and grand mal seizures may develop. Hallucinations and delirium may also occur between the third and eighth day. Barbiturate-induced delirium tremens is very similar to alcohol withdrawal DT's. Fever may develop within 36 to 72 hours and progress to severe hyperpyrexia. Normally, fever subsides after three to four days, and usually lasts no longer than a week.[15] These adverse effects may be lethal if treatment is not started within 24 to 72 hours of the last barbiturate dose. These patients may be best treated by persons with experience in handling drug withdrawal.

Phenobarbital is the standard drug for the treatment of barbiturate and sedative-hypnotic withdrawal syndromes.[15,17] Because of its long half-life (approximately four days), phenobarbital provides more constant serum levels than shorter-acting barbiturates. It also appears to cause less euphoria.[18] Once phenobarbital equivalents have been established (Table 1), stabilization on equivalent doses should be maintained for two days, after which a gradual withdrawal at a rate of 30 mg per day may be used.[17] This method is conservative. Other programs have varied the degree of tapering in dosage schedules. For example, rapid detoxification has been suggested, whereby daily decreases of phenobarbital are scheduled to be completed in ten days, regardless of the degree of tolerance.[15] No side effects were reported in 200 patients for whom the latter technique was used.

Benzodiazepine Drugs

The potential for benzodiazepine-induced physical and psychological dependence after continued use of generally prescribed doses (such as

TABLE 1.—*Equivalent Doses of Phenobarbital for Common Sedative-Hypnotic Drugs in Treating Withdrawal Symptoms**

Drug	*Sedative-Hypnotic Dose (mg)*	*Phenobarbital Equivalent Dose (mg)*
Barbiturates		
Amobarbital	100	30
Butabarbital	60	30
Pentobarbital	100	30
Secobarbital	100	30
Other sedative-hypnotic agents		
Chloral hydrate	500	30
Ethchlorvynol (Placidyl)	350	30
Glutethimide (Doriden)	250	30
Meprobamate (Equanil, Miltown)	400-600	30
Methaqualone (Quaalude, Sopor)	250-300	30
Methyprylon (Noludar)	300	30
Benzodiazepines		
Chlordiazepoxide (Librium)	100	30
Chlorazepate (Tranxene)	50	30
Diazepam (Valium)	50	30
Flurazepam (Dalmane)	60	30
Oxazepam (Serax)	100	30

*Table reprinted by permission from Khantzian and McKenna[15] (original data from Smith and Wesson[16]).

20 to 40 mg of diazepam per day) has been recognized.[19] After long-term use of 45 mg of diazepam per day, sudden cessation can produce withdrawal symptoms similar to those associated with long-term use of ethanol or barbiturates, including agitation and confusion.[20] Acute organic brain syndromes, seizures and coma have been reported.[20] Kales stated that rebound insomnia can be induced by the shorter-acting benzodiazepine agents, such as nitrazepam (not on the market in the United States), but not by diazepam or flurazepam.[21] Withdrawal symptoms are minimal for the first five days and peak between the fifth and ninth days. In patients taking large doses (about 300 mg per day) over a long time, the drug should be withdrawn slowly to minimize the likelihood of withdrawal seizures.[19] Gradual withdrawal from large doses should probably begin without interruption of the dosage schedule and continue for ten days.

Psychosis has been associated with sudden withdrawal of benzodiazepine drugs. However, in the cases reported, each patient had a prior history of psychiatric illness.[19,20,22] Generally, the onset of psychosis occurs three to eight days after withdrawal. Doses of less than 45 mg of diazepam per day in patients without histories of psychiatric illness caused minor abstinence syndromes, but no seizures or withdrawal psychoses were noted. Treatment of withdrawal psychosis consists of either readministration of the benzodiazepine agent or instituting pentobarbital as substitute therapy. Pentobarbital is a rapid-acting, sedative-hypnotic drug that produces cross tolerance with the benzodiazepine agent.[19] Reversal of the psychosis usually occurs within 24 to 48 hours as the patient becomes sedated.

Cimetidine

Since its introduction, cimetidine has been widely used in the treatment of gastrointestinal ulcerations and other disease states. In recent case studies abrupt ulcer perforations after cessation of therapy have been reported,[23,24] but rebound hyperacidity has not been shown conclusively. No firm evidence has established that abrupt or gradual withdrawal provokes a rebound effect.[25]

Clonidine

The sudden withdrawal of clonidine (0.2 mg or more per day) may precipitate rebound hypertension in a small percentage of patients. It is postulated that this condition results from excessive catecholamine release and stimulation of central alpha inhibitory receptors.[26] Clinical features include palpitations, headache, irritability and agitation and, occasionally, insomnia, tremors, nausea and severe vomiting. The resulting elevated levels of urinary vanillylmandelic acid and catecholamines as well as the pressor crisis may last as long as 17 days, but usually last for between 24 and 48 hours. Abrupt withdrawal causes blood pressure to increase to baseline, or rebound to pressures as high as 220 to 270 mm of mercury systolic and 140 to 160 mm of mercury diastolic, accompanied by tachycardia.[26,27] This crisis can be managed either by alpha-blocking drugs such as phentolamine or dibenzyline, taken concomitantly with propranolol, or by reinstitution of clonidine. In these circumstances it may be prudent for clinicians unfamiliar with the syndrome to consult with persons having previous experience in handling clonidine withdrawal syndromes. There have been two case reports of rebound hypertension from sudden withdrawal of methyldopa therapy of the same magnitude as occurs with clonidine cessation.[28,29]

Corticosteroids

Suppression of adrenal activity resulting from corticosteroid use is dependent on the dose, duration, frequency, time and route of administration

of the drug. Doses equivalent to 40 mg of prednisone administered for less than five to seven days infrequently result in appreciable pituitary-adrenal suppression.[30] In these instances, corticosteroids can be discontinued without provoking adrenal crisis. Any reduction in dosage, however, may result in exacerbation of the underlying disease.

Intensive, high-dose therapy for 48 hours is often used in the treatment of allergic emergencies, hypoglycemic coma, cerebral edema, vasculitis and other conditions. When the duration of therapy is 48 hours or less, abrupt discontinuation of the drug carries little risk of precipitating an acute adrenal crisis. This may also be true during treatment for up to five days. However, treatment with large doses for five days or more can cause some degree of impairment in the corticotropin stimulation response.[31] In one study, 13 of 14 patients taking 40 to 100 mg per m^2 of prednisone for 5 to 29 days had suppressed adrenal function for 24 hours. In five patients, this effect lasted seven days or more; however, no patient suffered adverse effects. Postmortem examinations have shown a decrease in the weight of adrenal glands in patients who had received corticosteroid therapy for five to ten days.[32] Supraphysiological doses administered for two weeks have disrupted the hypothalamic-pituitary-adrenal feedback mechanism in patients for as long as 12 months.[33] Therefore, it seems prudent to taper the doses of corticosteroids in patients who have received more than 40 mg of prednisone or its equivalent for more than five days. It is less clear whether one should taper these doses in patients who have been given corticosteroids for two to five days.

Prolonged drug therapy is frequently indicated for many diseases such as asthma and ulcerative colitis. Nearly all patients receiving this therapy (more than 15 mg of prednisolone), require gradual withdrawal to prevent acute secondary adrenal insufficiency.[30,33] An inability to respond appropriately to stress may still persist even after gradual reduction in dose. Administration of 15 mg to 120 mg of prednisolone daily for longer than 10 to 14 days may result in prolonged suppression of the hypothalamic-pituitary-adrenal axis.[30,34] However, patients taking less than 20 mg of cortisol or its equivalent (approximately 5 mg of prednisone) generally are able to respond to stress five months after abrupt discontinuation.[33] Alternate day therapy with intermediate-duration corticosteroids does not interfere with stress response. Where the axis has been suppressed the hypothalamic-pituitary complex usually recovers before the adrenal gland's ability to respond.[34] Attempts to hasten recovery with adrenocorticotropic hormone (ACTH) stimulation have been unsuccessful.

Reduction of the daily dose of prednisone by 2.5 to 5.0 mg every three to seven days is a reasonable approach to gradual tapering.[30] This is a cautious approach, which may be preceded by rapid tapering to physiological doses, provided that flares in the disease do not occur. Thereafter, a more gradual approach is required. Rheumatoid arthritis is an exception to this rule, in that exacerbation often occurs secondary to rapid corticosteroid tapering. During periods of minor stress such as a mild infection, an additional 100 mg per day of hydrocortisone or its equivalent (25 mg of prednisone) should be administered. In cases involving major trauma or surgical procedures, the equivalent of 200 to 300 mg per day of hydrocortisone should be given for as long as 6 to 12 months after cessation of long-term corticosteroid therapy.[30]

To ensure that a patient's adrenal status remains intact, one or both of the following tests may be done. After withholding the morning dose, an 8 AM measurement of plasma cortisol is obtained. A level greater than 10 μg per dl implies that the baseline pituitary-adrenal function is adequate. Or, one may administer 250 μg of synthetic ACTH (cosyntropin) after measuring the baseline cortisol level, to determine the rise in plasma cortisol after 30 to 60 minutes. An increase in plasma cortisol levels of greater than 6 μg per dl, resulting in a level higher than 20 μg per dl is considered to be normal. When this response is observed, corticosteroid therapy can be discontinued.[30,34]

Opiates

Opiate withdrawal is rarely life threatening. The severity of withdrawal symptoms depends on the particular opiate used, the dose and duration of use, and the underlying diseases. Although withdrawal symptoms from various opiates are similar, their onset, duration, and severity vary among preparations. Anxiety, yawning, rhinorrhea, lacrimation, diaphoresis, shaking, chills and piloerection (thus "cold turkey"), anorexia, nausea, vomiting and abdominal cramps begin 6 to 12 hours after the abrupt discontinuation of heroin or morphine.[35] Then after 48 to 72 hours, central nervous system excitation, restlessness,

insomnia, muscle spasms, and low back pain occur. Elevated blood pressure, tachycardia, dehydration, ketosis and leukocytosis are common. Symptoms usually subside in five to ten days.

The meperidine withdrawal syndrome begins within 3 hours, peaks in 8 to 12 hours, and lasts three to five days. Apparently, in meperidine withdrawal there are fewer gastrointestinal symptoms; but more severe symptoms of restlessness and muscular twitching than from other opiate abstinence syndromes.[36] The longer-acting methadone produces symptoms beginning 36 to 72 hours, peaking in intensity in 6 days, and subsiding 10 to 14 days after drug discontinuation. The withdrawal syndrome has also occurred in patients who have abstained from high-dose pentazocine,[37,38] or propoxyphene use.[39,40]

In deciding on specific interventions to treat opiate withdrawal, methadone is the drug of choice because of its ability to block the symptoms without producing euphoric effects.[17] Others have used diazepam, chlorpromazine and LAAM (l-α-acetylmethadol) to manage opiate withdrawal symptoms.[41]

To stabilize the condition of a patient who is suffering from withdrawal symptoms, 10 to 20 mg of methadone should be given orally every two to six hours as symptoms persist. It is not unusual to find that 80 to 180 mg per day are needed as an initial stabilization dose. This initial dose should be maintained for two to three days. Also, 1 mg of methadone can be substituted for 4 mg of morphine, 2 mg of heroin or 20 mg of meperidine.[42]

The length of time provided for a gradual tapering of methadone varies among health centers. Prolonged withdrawal has been accomplished by reducing the methadone stabilizing dose by 20 percent each day.[17] Patients taking smaller doses (40 mg per day) can proceed with daily reductions of 5 to 10 mg increments without complications.[15] Complete, gradual withdrawal in patients who have been receiving more than 100 mg per day may take as long as a month. Most health centers use the gradual withdrawal method in one form or another.

Methadone should be withdrawn gradually because its use produces physical dependence. The symptoms induced by methadone withdrawal are similar to those of the other opiates and begin 36 to 72 hours after discontinuance. Methadone withdrawal differs from withdrawal from other opiates in that the former does not produce muscle aches, cramps, signs of autonomic dysfunction, nausea or vomiting. Reports conflict concerning the difference in severity of withdrawal symptoms between methadone and other opiates—some claim that methadone has more gradual and less severe symptoms than other opiates,[17] while others state that methadone produces excruciating withdrawal symptoms greater than other opiates.[43] Recent literature has suggested that the withdrawal symptoms from methadone are more severe than those from heroin, especially in newborn infants.[44]

Circumstances such as arrest or admittance to hospital have led to abrupt cessation of methadone maintenance therapy. In some patients, no symptoms occur after such sudden termination,[45] while in others generalized pain and insomnia have been reported. Almost no symptoms are present two weeks after withdrawal.

The most serious opiate withdrawal symptoms occur in newborn infants of addicted mothers. The onset of withdrawal is determined by the following factors: (1) the time of drug administration before delivery, (2) the amount of the drug consumed, (3) the presence of other drugs in the mother's serum and (4) the metabolism and excretion of the opiate by the infant. Not all infants will suffer withdrawal symptoms. The prevalence of this phenomenon has been estimated to be between 50 percent and 91 percent.[46,47] Symptoms of heroin withdrawal usually begin in the first 24 to 48 hours, while signs of methadone withdrawal can begin during the first four days of life. Careful monitoring of newborn infants is necessary because symptoms may be mild during the first few days, and progress in severity between the 7th and 14th days.

Heroin and methadone cause similar withdrawal symptoms in newborn infants. They can include abrasions, clonus, pronounced tremors, convulsions, decreased sleep time, vomiting, high-pitched cry, respiratory distress and fever. Severe symptoms can lead to profuse vomiting, dehydration with acidosis, and death. Infants of mothers addicted to methadone usually suffer more severe and prolonged symptoms compared with infants of mothers addicted to heroin.[44,46,47] The prevalence of seizures seems to be greater for infants withdrawing from methadone. Among 384 infants of heroin-addicted mothers, only 8 were observed to have seizures, while in 46 infants of methadone-addicted mothers, 5 had seizures.[47] Mortality has ranged between 34 percent and 93 percent.[44] The latter figure represents untreated

infants. Signs of pentazocine withdrawal occur 10 to 20 hours after birth,[38] approximately the same onset as propoxyphene-induced complications. Several treatment protocols have been established involving a variety of drugs, including paregoric, chlorpromazine, diazepam and phenobarbital. The discussion of each treatment modality is beyond the scope of this paper; however, these regimens have been fully described elsewhere.[44,46,47]

Propranolol

The existence of a rebound phenomenon associated with the abrupt cessation of propranolol in patients with coronary artery disease has been supported and denied.[48-50] Abrupt withdrawal in patients taking 80 to 320 mg per day was reported to cause an increased prevalence of chest pains, arrhythmias, acute myocardial infarctions and sudden death.[49] In one double-blind study involving 20 patients with stable angina pectoris, abrupt withdrawal resulted in one fatal myocardial infarction, one episode of ventricular tachycardia and four cases of increased anginal symptoms. The withdrawal phenomenon was more prominent in patients who had gained the most antianginal benefit from the drug and who exhibited the most severe initial symptoms. Abrupt withdrawal of a placebo resulted in anginal symptoms in 4 of 14 patients.

One retrospective study involved 102 patients who had taken at least 80 mg per day for three months or more and who had had catheterization.[48] The results failed to show any significant difference in the prevalence of death or MI's, or significant change in chest pain between a group withdrawing from propranolol use and a control group in whom propranolol therapy was continued. It appears that the actual prevalence of a rebound phenomenon is unknown. A possible rebound reaction may be clouded by intensified symptoms induced by changes in physical exertion.[49]

Shenkman and co-workers reported three cases of hyperthyroidism developing in a group of patients with no prior history of thyroid disease 1 to 12 weeks after discontinuation or reduction in dosage of propranolol.[51] Withdrawal tachycardia, sweating or tremors correlated with increases in serum triiodothyronine (T_3) in another study.[52]

The mechanism of a rebound reaction has not been fully elucidated. Several possible explanations include (1) stimulation of hypersensitive beta-adrenergic receptors,[53,54] (2) a shift of oxyhemoglobin dissociation (favorable rightward displacement occurs with propranolol), (3) reactivation of the renin-angiotensin-aldosterone mechanism, (4) increased platelet aggregation[48] or (5) an increased sympathetic tone unmasked on cessation of beta blockade. Nattel and co-workers observed that in some patients a hypersensitivity to the chronotropic effects of isoproterenol beginning four days after propranolol treatment was precipitously discontinued, and lasting six days (mean values).[54] This hypersensitive response may be due to increased numbers of adrenergic receptors acquired during propranolol therapy, to increased responsiveness of receptors or to elevated plasma catecholamine concentrations. This hypersensitivity appears to be the most plausible mechanism for the propranolol rebound reaction at this time, although each explanation may play a role in the development of the syndrome. Other mechanisms have not been explored as extensively as the hypersensitivity phenomenon.

Generally, propranolol is discontinued abruptly 12 to 48 hours before surgical procedures to avoid additive myocardial depressant effects with anesthetic medication. Few adverse effects resulting from this practice have been reported.[55] In patients with severe coronary artery disease who require cardiac procedures, however, tapering the dose of propranolol over a few days seems reasonable. Other beta-blocking agents have also been reported to cause the rebound phenomenon.

Stimulants

The abstinence syndrome associated with amphetamines, methylphenidate and fenfluramine is marked by lethargy, sleep disturbances and prolonged depression.[15,56,57] Depression is perhaps the most significant symptom; admittance to hospital and therapy with tricyclic compounds generally have been advocated. Use of tricyclic antidepressant drugs in treating patients who are not in hospital and who are known to be drug abusers may be hazardous, however. No controlled study has definitely shown that the tapering of stimulants reduces the severity or duration of withdrawal symptoms.

Tricyclic Antidepressant Medication

Abstinence symptoms due to tricyclic compounds have been reported most often after the abrupt withdrawal of imipramine.[58-61] Only a few case reports have described withdrawal from

desipramine[59] and amitriptyline.[62] Administration of 75 to 375 mg per day of imipramine and 30 to 50 mg per day of amitriptyline for at least two weeks provoked symptoms when abruptly terminated. Symptoms invariably occurred within 24 to 48 hours. The occurrence of withdrawal symptoms in 45 patients was as follows: nausea with or without vomiting in 16, headache in 10, giddiness in 10, chills in 6, weakness and fatigue in 5 and musculoskeletal pain in 4.[61] Of 26 patients treated with imipramine for longer than two months, 22 reported symptoms after discontinuation, while only 3 of 19 patients treated with the same dosage range for less than two months reported similar symptoms on discontinuation of treatment. In one group of 13 patients in whom imipramine therapy had been tapered in less than two weeks, 8 had pronounced and 5 had minimal symptoms. In another group of 13 patients drug doses were tapered for longer than two weeks. In two patients pronounced withdrawal symptoms developed; none complained of mild symptoms. It appears, then, that tricyclic compounds should be tapered over no less than two weeks.

An akathisia-like syndrome has been reported with discontinuation of imipramine use in several patients.[60] This consisted of anxiety, motor restlessness and inability to sit still, which was indistinguishable from akathisia induced by antipsychotic agents. This syndrome appeared when imipramine therapy was abruptly stopped, and disappeared when therapy was reinstituted.

Withdrawal symptoms have appeared in newborn infants of mothers taking tricyclic drugs. Symptoms include breathlessness, cyanosis, tachypnea, tachycardia, wakefulness, irritability and profuse sweating, and develop one to five days after birth. The mothers reported taking 50 to 150 mg of tricyclic drugs per day throughout their pregnancies.[58]

Other Drugs

Other drugs have been reported to cause withdrawal symptoms, but do not meet the criteria listed above. These include azathioprine,[63,64] baclofen,[65,66] cromolyn,[67,68] nitroprusside,[69] antithyroid drugs,[70,71] aminocaproic acid,[72,73] methaqualone,[74] lithium[75,76] and phenelzine.[77]

Conclusion

Although many drugs are considered to cause withdrawal syndromes, few have been adequately studied in this context. The sedative-hypnotic agents, corticosteroids, stimulants, clonidine and tricyclic antidepressant drugs have met one of the criteria for drug withdrawal syndromes as listed above. Other compounds have been reported to cause rebound symptoms in limited numbers of cases. Until further experience bears out that abstinence syndromes result from these agents, no definite recommendations for drug discontinuation (such as before operations or drug holidays) can be made. Nonetheless, precaution should be taken when terminating therapy with drugs for which numerous reports of rebound phenomena exist.

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