WITHDRAWAL SYMPTOMS FOLLOWING DISCONTINUATION OF IMIPRAMINE THERAPY [1]

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On discontinuation of imipramine [5] treatment some psychiatric patients reported nausea, vomiting, dizziness, coryza, muscular pains and malaise. The symptoms were first regarded as conversion phenomena, but after several repetitions were considered due to physiological withdrawal.

Of the patients treated with imipramine 45 had been observed within the hospital during withdrawal of medication. Treatment was instituted with oral doses of 75 mg. daily and usually increased each week in 75 mg. steps. The daily maintenance dose was 300 mg./day in 34 patients, more than 300 mg./day in 3 patients, and less than

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[5] The cooperation and assistance of Geigy Pharmaceuticals is gratefully acknowledged.

300 mg./day in 8 patients.

We reviewed our interview records and the daily nursing notes, noting reports of withdrawal symptoms within 48 hours of cessation of medication in 25 of the 45 patients. Most prominent were nausea with or without vomiting—16 subjects, headache—10, giddiness—10, coryza—8, chills—6, weakness and fatigue—5, and musculoskeletal pain—4.

Twenty-two of 26 patients treated for 2 months or longer reported withdrawal symptoms, while only 3 of 19 patients treated less than 2 months reported similar symptoms ($p<.001$).

The 25 patients who had been treated for more than 2 months were rated for severity of symptomatology. The reaction was scored as "marked" if subjects reported more than 2 different symptoms with significant distress and as "minimal" if they reported fewer than 2 symptoms causing minor distress, or no symptoms. Of 13 patients with a medication tapering and termination period of less than 2 weeks, 8 had marked withdrawal symptoms and 5 minimal. Of 12 with a medication termination period longer than 2 weeks, only 2 subjects demonstrated marked withdrawal symptoms ($p=.05$).

These results are in keeping with the general experience that the intensity of physiological withdrawal symptoms is directly proportional to the duration of drug administration and the abruptness of withdrawal. We could not relate the withdrawal syndrome to the size of the maintenance dose, since our range was too small. However, our modal schedule of 300 mg. per day is larger than the usual clinical schedule of 100 to 150 mg. per day and may account for the inconspicuousness of this phenomenon in other studies.

We observed that allowing a period of 2-4 weeks for withdrawal was prophylactically effective. When symptoms on imipramine discontinuation occurred they could readily be treated by resuming imipramine at 50 mg. daily and gradually decreasing over a 1-week period.

Discussion

A physiological withdrawal syndrome following the termination of treatment with opiates, demerol, barbiturates, glutethimide, alcohol, chlorpromazine and meprobamate is well known. Recently withdrawal symptoms with methaminodiazepoxide(2), nialamide(1) and alpha-ethyltryptamine(5) have been reported. Kuhn(3) and Mann and Macpherson(4) have also reported symptoms on abrupt imipramine withdrawal.

Until recently the physiological withdrawal syndrome was considered restricted to CNS "depressants" such as opiates, barbiturates and alcohol. This was confirmed by the absence of such a syndrome with "stimulant" drugs such as cocaine, d-amphetamine, marijuana, mescaline and LSD. The occurrence of such a syndrome with imipramine, nialamide, and alpha-ethyltryptamine is of considerable interest, therefore, since these drugs have been loosely referred to as "psychic energizers" with energetic effects similar to "stimulant" drugs. It is apparent that a simple depression-stimulation dimension is inadequate to describe the complexity of drug effect both physiologically and behaviorally.

The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety." This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability.

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Withdrawal Symptoms Following Discontinuation of Imipramine Therapy

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On discontinuation of imipramine treatment some patients, under observation for a variety of psychiatric syndromes, reported nausea, vomiting, dizziness, coryza, muscular pains and malaise. The symptoms were first regarded as conversion phenomena, but after several repetitions we considered these to be due to physiological withdrawal and an attempt was made to determine their frequency and variety.

Of the patients treated with imipramine during an eighteen month period, forty-five had been observed within the hospital setting during withdrawal of medication. In these subjects treatment was instituted with oral doses of 75 mg daily and usually increased each week in 75 mg steps. The daily maintenance dose was 300 mg/day in thirty-four patients; more than 300 mg/day in three patients; and less than 300 mg/day in eight patients.

We reviewed our interview records and the daily nursing notes, noting reports of withdrawal symptoms within 48 hours of cessation of medication in 25 of the 45 patients. (Table I)

TABLE I

Table I

Symptoms Within 48 Hours of Cessation of Imipramine Therapy

Patients ceasing therapy	45
Patients reporting symptoms	25

Symptoms

Nausea (and/or vomiting)	16
Headache	10
Giddiness	10
Coryza	8
Chills	6
Weakness or faintness	5
Musculo-skeletal pain	4

A significant relationship is evident when the duration of treatment and the appearance of symptoms are compared. (Table II) Twenty-two of twenty-six patients treated for two months or longer reported withdrawal symptoms, while only three of nineteen patients treated less than two months reported similar symptoms.

TABLE II

To determine the relation of the abruptness of medication withdrawal to induced symptoms, the twenty-five patients who had been treated for more than two months were rated for severity of symptomatology. The reaction was scored as "marked" if subjects reported more than two different symptoms with significant distress and as "minimal" if they reported fewer than two symptoms causing minor distress, or no symptoms. Two groups were defined according to whether the period of medication reduction was less than two weeks or two weeks or longer. (Table III)

TABLE III

Table II

Duration of Imipramine Therapy

	Withdrawal Symptoms (subjects)	No Withdrawal Symptoms (subjects)
Less than Two Months	3	16
Two Months or Longer	22	4

$x^2 = 23.94$

$p < .001$

Table III

Period of Drug Cessation in Patients Treated at Least Two Months

	Withdrawal Symptoms	
	Marked	Minimal
Less than Two Weeks	8	5
Two Weeks or Longer	2	10

$p = .05$ (Fisher) (4)

These results are in keeping with the general experience that the intensity of physiological withdrawal symptoms is directly proportional to the duration of drug administration and the abruptness of withdrawal. We could not relate the appearance of the withdrawal syndrome to the size of the maintenance dose, since our range was too small. However, our modal schedule of 300 mg per day is larger than the usual clinical schedule of 100 to 150 mg per day and may account for the inconspicuousness of this phenomenon in other studies. It must be noted that withdrawal symptoms were reported by one patient who was treated for two months at a maximum dose of 75 mg per day.

We observed that allowing a period of 2-4 weeks for withdrawal was prophylactically effective. When symptoms on imipramine discontinuation occurred they could readily be treated by resuming imipramine at 50 mg daily and gradually decreasing over a one week period.

Discussion

The occurrence of a physiological withdrawal syndrome following the termination of treatment with opiates, demerol, barbiturates, glutethimide and alcohol is well known. Recently withdrawal symptoms with chlorpromazine (2), methaminodiazepoxide (7), nialamide (5), alpha-ethyltryptamine (9) and meprobamate (1,3,6) have been reported. Kuhn (8) has also observed symptoms on abrupt imipramine withdrawal.

Until recently the physiological withdrawal syndrome was considered restricted to CNS "depressants" such as opiates, barbiturates and alcohol. This was confirmed by the absence of such a syndrome with "stimulant" drugs such as cocaine, d-amphetamine, marijuana, mescaline and LSD. The occurrence of such a syndrome with imipramine, nialamide, and alpha-ethyltryptamine is of considerable interest, therefore, since these drugs have been loosely referred to as "psychic energizers" with energetic effects similar to "stimulant" drugs. It is apparent that a simple depression-stimulation dimension is inadequate to describe the complexity of drug effect both physiologically and behaviorally.

The withdrawal syndrome complicates the evaluation of patients after drug discontinuation, both clinically

and experimentally, since both patients and physicians often interpret the onset of malaise, faintness, etc. as an upsurge of "anxiety" related to incipient relapse, and hasten to resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability.

Summary

1. The termination of imipramine treatment produces physiological withdrawal symptoms, which are related to length of treatment and abruptness of withdrawal. Symptoms may also be related to dosage level.

2. Withdrawal symptoms may be minimized or eliminated by weaning techniques.

3. The occurrence of a withdrawal syndrome with imipramine is pertinent to the conceptualization of its psychopharmacological activity, and to problems of clinical management.

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