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Opioid Withdrawal and Naltrexone Induction in 48–72 Hours with Minimal Drop-out, Using a Modification of the Naltrexone-Clonidine Technique

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Using clonidine, naltrexone, and diazepam, 60 withdrawals from heroin and other opioids involving 56 addicts were carried out with only one patient dropping out. In the last 23 cases, we used a modification of the standard technique, giving significantly higher doses of naltrexone and clonidine on the first day. This significantly reduced the average withdrawal time from 3.30 days to 2.32 days, despite lower clonidine dosage and significantly lower diazepam dosage on the second day. The speed, effectiveness, economy, and high acceptability of this withdrawal technique have implications for both private and state-funded treatment programmes.

Opiate withdrawal is generally a comparatively lengthy process. Two or three weeks for in-patients, and 8 weeks or more for out-patients are still the rule for methadone substitution and withdrawal programmes, but in a recent British study (Gossop *et al*, 1987) 6 out of 25 in-patients and 24 out of 29 out-patients failed to complete withdrawal. Such figures are not atypical. Apart from the high subsequent relapse rate of detoxified opiate addicts recorded in many studies, this order of drop-out represents a significant waste of medical and nursing time and facilities.

Clonidine attenuates the severity of opiate-withdrawal symptoms (Gold *et al*, 1978) and can reduce the average time of in-patient methadone withdrawal to 9 or 10 days. Combining clonidine with opiate antagonists accelerates withdrawal without increasing the overall severity of withdrawal symptoms compared with clonidine treatment alone (Charney *et al*, 1982). The rationale is that antagonists compress the withdrawal symptoms into 2 or 3 days, enabling them to be treated energetically with appropriate medication and psychological support. Using clonidine and naltrexone, aided by moderate doses of sedatives, detoxification even from methadone has been regularly accomplished in 3–5 days. If clonidine is not used, patients must usually wait 7–10 days after their last dose of methadone and 5–7 days after heroin before starting naltrexone. Not surprisingly, many addicts relapse during this period (Kleber, 1985).

Between December 1985 and May 1987, we carried out 60 detoxifications on 56 patients, using clonidine and naltrexone. Until March 1987, we followed the method described by Kleber & Kosten (1984). On this regime, most patients were able to be discharged home taking a full 50 mg dose of naltrexone 3–4 days after admission. However, even 4 days of private in-patient care can be a severe strain on uninsured families. Encouraged by the findings of Charney *et al* (1986), we reviewed our practice with the aim of further reducing the duration of in-patient treatment, starting naltrexone earlier and using higher doses of clonidine. This paper describes our experience with two schedules for withdrawal. It is the first detailed British report of the clonidine–naltrexone technique and is the largest reported series.

Method

Most patients were referred by various voluntary agencies or sought help directly after hearing about our programme from other opiate abusers. Clinical and social data for the two groups are given in Table I. At this time, we were not offering methadone maintenance, and all patients came specifically for withdrawal, and subsequent treatment with family-supervised naltrexone. None was hypertensive or had any contraindication to treatment with clonidine, and all were accepted. They form, accordingly, a consecutive sample. Most patients used opiates in their usual dosage until a few hours before admission, but several tried to cut down, while others had a final 'opiate binge'. Maintenance opiates were prescribed for only three patients, who had jobs and needed time to arrange their affairs before admission. Four patients – two in each group – were detoxified a second time after resuming opiate abuse at least 4 weeks after their initial detoxification.

Group A (37 patients)

After physical examination, an initial test dose of clonidine (0.1 mg) was given, and repeated after 2 h to exclude

TABLE I
Social and clinical characteristics of patients

	Group A	*Group B*
Mean age (range)	26.5 (17–55)	29.5 (18–41)
Percentage female	26	17
Percentage received previous treatment	71	52
Percentage with drug-related convictions	63	48
Average length of opiate abuse (years)[1]	5.3 (0.7–10)	4.5 (0.7–12)
Average daily heroin use (as 'street' heroin)[2]	0.59 g[3] (s.d. 0.50)	0.78 g (s.d. 0.47) $t=1.12$, d.f. 33 (NS)
Percentage injecting opiates	44.7	45.5

1. Three patients dependent on methadone, one each on pethidine, butorphanol, and morphine.
2. Believed to contain currently about 20–30% pure diamorphine.
3. Average for 17 patients for whom full withdrawal prescribing information was available.

undue sensitivity to its hypotensive effect, defined as a drop in blood pressure to less than 80/55. Patients were asked to report immediately any significant withdrawal symptoms, and were offered further clonidine (0.2–0.3 mg) 4-hourly as needed. If this gave inadequate relief, diazepam (as advised by Kleber & Kosten, 1984, although we used higher maximal doses) was offered in addition. At night, patients received nitrazepam or flurazepam if necessary. Naltrexone was usually started only on the second day, or during the afternoon of the first day, if the patient had been admitted in the morning. We wanted to avoid precipitating withdrawal symptoms during the evening or night when medical and nursing cover is less intensive. Initial naltrexone dosage was 1 mg, repeated 4-hourly and increasing to 2 mg if withdrawal symptoms were well controlled.

At the doses used in withdrawal, clonidine often has a sedating effect. The response to naltrexone was variable. Some patients had few withdrawal symptoms and needed little or no diazepam. In contrast, others experienced significant discomfort and required maximal doses of clonidine and diazepam. However, only one patient failed to complete withdrawal. Detoxification was deemed to have occurred when the patient had received at least a normal maintenance dose of naltrexone (50 mg) in a 24 h period and felt well enough to return home.

Where the prescribed dosage was flexible within a given range, the precise dose administered was not always noted on the drug-administration record used for the first 20 of the 37 patients in Group A. Complete information was available for the remaining 17 patients in Group A (and all 23 patients in Group B).

Group B (23 patients)

These patients were encouraged to arrive early in the day and received a test dose of clonidine (0.2 mg) as soon as possible after admission and brief preliminary cardiovascular examination. No patient became hypotensive on this dosage. After 1 h, a further 0.1 mg of clonidine was given, and after another 45 min, the first dose of naltrexone (1 mg). Charney *et al* (1986) administered naltrexone at 4-hourly intervals, increasing by 1 mg increments on day 1 and by 2 mg on day 2 if well tolerated. We have modified this schedule. Naltrexone was given every 90 min. If well tolerated, each dose was progressively increased to 2 mg and then 5 mg, the last dose of the day usually being given about 1800 h. Conversely, if withdrawal symptoms were distressing, we withheld naltrexone until they were adequately controlled with clonidine and, if necessary, diazepam. We gave clonidine regularly every 2 or 4 h to a maximum of 0.4 mg in any 4 h period, unless BP fell below 80/55. Following Kleber & Kosten, we sometimes used oral or intramuscular hyoscine in addition if abdominal cramping or nausea were troublesome.

Results

The average time for detoxification was 3.30 days for all 37 patients in Group A (range – to the nearest 12 h – 2–5 days, s.d. 0.87) and 2.32 days for Group B (range 1–3 days, s.d. 0.68). $t=1.81$; d.f., 59; $P<0.05$. The average doses of clonidine, naltrexone, and diazepam (and the dose range) for the 17 patients in Group A for whom full details of medication were available, and all 23 patients in Group B, during the first two 24 h periods, were as follows.

Day 1

Clonidine

A, 0.64 mg (0.3–1.2), s.d. 0.23; B, 1.22 mg (0.8–1.6), s.d. 0.24.
$t=7.59$; d.f. 38, $P<0.0005$ (one-tailed).

Diazepam

A, 64.7 mg (30–130), s.d. 35.9; B, 75.4 mg (40–180), s.d. 37.2.
$t=1.00$; d.f. 39 (NS).

Naltrexone

A, 3.3 mg (1–7)[1], s.d. 1.89; B, 20.9 mg (5–50), s.d. 13.77.
$t=3.98$; d.f. 31, $P<0.0005$.

Day 2

Clonidine

A, 0.84 mg (0.3–0.9), s.d. 0.18; B, 0.70 mg (0.2–1.3), s.d. 0.30.
$t=1.41$; d.f. 36; $P<0.1$ (NS).

1. $n=10$ – the other seven patients did not receive naltrexone until Day 2.

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Diazepam

A, 67.6 mg (35–140), s.d. 33.47; B, 38.7 mg (10–110), s.d. 23.46.
$t = 2.78$; d.f. 38; $P < 0.001$.

Naltrexone

A, 14.7 mg (2–50)[2], s.d. 14.37; B, 46.7 mg (14–50)[3], s.d. 9.23.
$t = 8.29$; d.f. 35; $P < 0.0001$.

Discussion

Charney *et al* (1986) describe their method as allowing ". . . flexible, individualised clonidine and naltrexone administration . . . ". The degree of flexibility is evidently even greater than their findings indicate. By using higher doses of clonidine and naltrexone and adding, especially on day 1, individualised doses of diazepam no greater than those commonly used in alcohol withdrawal (Sellers *et al*, 1983), most patients can be withdrawn from heroin or methadone within 3 days. This small modification gives significantly improved results. While few of our patients were taking methadone, they did not in general seem to need longer than patients withdrawing from heroin. Charney *et al* (1986) note that ". . . there did not appear to be a clear relationship between methadone dose and duration of [withdrawal] . . . " and Kleber *et al* (1987) state that "clonidine–naltrexone . . . appears to equalise the length of the heroin and methadone withdrawal symptoms".

Although one might expect a more rapid withdrawal programme to have a higher drop-out rate, only one patient failed to complete the programme, and he was one of the early subjects in Group A who used 2 g of street heroin daily. This is an even higher success rate than the 38 out of 40 reported by Charney *et al* (1986) – itself a figure that, as they point out, ". . . is equal to or higher than that of other standard methods and is achieved in a much shorter time". An important advantage of naltrexone in withdrawal is that even if minor withdrawal symptoms persist for a few days, the prolonged opiate-blocking effect of naltrexone – up to 72 h – prevents patients from obtaining relief by immediately resuming opiate use and thus perpetuating their dependence.

It is interesting that there was little difference between the groups in the average dose of diazepam on Day 1, but significantly less diazepam use in Group B on Day 2, despite its higher average daily heroin use. We think this reflects the significantly greater doses of clonidine on Day 1 and of naltrexone on Days 1 and 2 and our policy of deliberately concentrating both the withdrawal syndrome and our intensive treatment of it into the first day. At first we were concerned about hypotension and bradycardia, but, with increasing experience, we found, as did Kleber & Kosten, that they rarely occurred, responded quickly to reducing the dose of clonidine, and were of little clinical significance. The fact that the more rapidly detoxified and more heavily addicted group actually needed less clonidine on day 2 supports the hypothesis that naltrexone rapidly normalises the number and sensitivity of opiate receptors and reverses opioid-induced central noradrenergic hypersensitivity (Kleber *et al*, 1987).

Since the average daily dose of diazepam declined very much more quickly in Group B, the objections to using sedatives in opiate withdrawal are correspondingly reduced. (On day 3, the average for Group A, 44.1 mg, was still higher than the average for day 2 in Group B.) Some patients took small doses of clonidine – 0.1–0.2 mg three times daily – after discharge for a few days for persisting discomfort. This was significant in four cases, although not sufficient to delay discharge. However, we rarely prescribed benzodiazepines after discharge, except for sleep.

In the past, narcosis with thiopentone and paraldehyde or intramuscular chlorpromazine was sometimes used to get addicts through the worst of the withdrawal symptoms (Kleber & Riordan, 1982). This method has undeniable attractions for addicts afraid of withdrawal, but heavy sedation may be needed for several days. Narcosis can be hazardous and requires intensive nursing care. Phenothiazines may antagonise clonidine (Van Zwieten, 1977). We chose diazepam from the available benzodiazepines mainly because it is also available in rectal and parenteral preparations, which are useful if vomiting is a problem. The doses used do not constitute narcosis. Patients were always rousable and did not need intensive nursing. However, several patients had only a hazy recollection of the first treatment day. None thought this a bad thing.

The speed, effectiveness, economy, and very low drop-out rate of this method of withdrawal has major implications for treatment programmes in both the NHS and the private sector. It could considerably increase present detoxification facilities without any increase in beds and with a reduced

2. $n = 17$.
3. $n = 23$.

drop-out rate. It greatly reduces the necessity for the usual screening of visitors. Indeed, it questions the need for special in-patient units for detoxifying opiate addicts. At the Stapleford Unit, patients are treated in single rooms of a small private general psychiatric clinic, and some patients have been satisfactorily withdrawn in a private medical and surgical clinic by nurses and junior doctors without specialised training in psychiatry or addiction. Five were withdrawn at home under family supervision with the help of telephoned instructions and a visiting nurse or an electronic sphygmomanometer (Brewer, 1987).

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