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The Use of Propoxyphene Napsylate in the Treatment of Heroin and Methadone Addiction

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The use of methadone in the treatment of heroin addiction continues to be controversial. Propoxyphene napsylate (Darvon N®) is a possible alternative and a pilot study was conducted to test its acceptability, safety and clinical efficacy in treating long term, "multi-relapse" heroin addicts.

Findings indicate that propoxyphene napsylate suppresses many of the symptoms associated with opioid withdrawal phenomena. It should be viewed as a very promising therapeutic tool to be used in conjunction with psychological counseling and socio-vocational rehabilitation in detoxification and maintenance therapy for heroin or methadone addiction.

STIMULATED BY THE continuing controversy about the use of methadone in the treatment of heroin dependence, there has been much interest recently in finding a substance with the beneficial effects of methadone but without its undesirable characteristics. Initial research by Tennant[1,2] has suggested that propoxyphene napsylate (Darvon N®) may be an effective and safe substitute for methadone in both maintenance and detoxification therapy.

Pioneering methadone research by Nyswander and Dole[3-6] encouraged the establishment of a multitude of methadone treatment programs throughout the United States. Unfortunately, methadone has proved to be yet another physically addicting opioid drug which, moreover, is associated with pronounced withdrawal phenomena. Also, the much longer biological half-life of methadone, compared with that of other opiates, is seen to produce prolonged and complicated overdoses.[7-11] These problems, plus reports of lessened libido and male impotence,[1] have reduced the acceptance of methadone by the heroin addict population.

Tennant[1] has noted that in the Black population of the Watts area in Los Angeles, one response to this controversy has been an almost "evangelical acceptance" of propoxyphene napsylate (PN) therapy. Moreover, in a nine-month study, he found that PN had specific advantages over methadone for use in the treatment of heroin addiction. Of a total of 372 persons addicted to heroin, 230 were reported to be satisfactorily detoxified as inpatients, 50 were detoxified as outpatients and 92 were maintained (for a period of greater than 21 days) on PN as outpatients. Initial daily dosages of PN ranged from 300 mg to 1,600 mg, and although most were well above the recommended maximum daily dose of 8 mg per kg of body weight,[12] no toxicity was noted. He noted that therapy with PN not only had all the benefits of methadone therapy but, further, produced minimal

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physical addiction, resulted in no reports of impotence, induced an "unpleasant euphoria" (thus lending to negligible incidence of voluntary abuse), could not be injected, produced unpleasant effects when ingested simultaneously with other commonly abused drugs and had a low overdose potential. Of special interest were fairly consistent (71 percent) reports of a diminished or absent "yen" (craving for heroin) with PN therapy. The theme of "something works with PN" was repeatedly expressed by the population of this study.

Tennant's success has been paralleled by Bergin* in Sacramento. This research consisted of a well controlled, five-day inpatient PN detoxification program. Bergin's four-month, 178-patient study used much smaller doses of PN (an average daily high dose of 747 mg) than were used in Tennant's study. PN was administered in multiple daily dosages (100 to 200 mg four to six times per day) based upon observed withdrawal symptoms. No distinguishable side effects from PN were noted in any of the 178 patients. Bergin concluded that PN produced no physical dependence over this short period of administration and could be considered a safe drug when dispensed in the manner described. In addition, this study population (73 percent White, 14 percent Black and 10 percent Chicano, ranging from age from 18 to 48 years) was found to have a favorable attitude toward the use of PN for detoxification. Furthermore, the patient treated with PN was found to be more receptive to direct individual and group counseling. Emphasizing that a "varied support" of the client should be continued as the major part of therapy, Bergin nevertheless recognized PN to be a key drug in his methods of treating heroin addiction.

Recent investigation by List,* in Baltimore, has documented the effectiveness of PN in the detoxification of methadone patients. In using methadone for heroin detoxification in recommended decremental dosage alone, List observed severe opioid-like withdrawal symptoms. Patients had difficulty keeping jobs and there were abrupt social and personality changes when methadone dosage was decreased to 30 to 50 mg per day. Because of this observed phenomenon, a study of 80 patients (89 percent male, with 50 percent Black and 50 percent White) was arbitrarily divided into two treatment groups. One group was detoxified by decreasing methadone from established maintenance levels in decrements of 5 mg per week, and the second group was given 200 mg of PN in addition to 45 mg of methadone. Amounts of PN were then increased or maintained during detoxification as methadone dosage was decreased by 5 mg per week. After successful methadone detoxification, PN was then gradually reduced. Findings indicated that 33 percent of the patients receiving PN were successfully detoxified, compared with only 6 percent of the group treated with methadone alone. It was also noted that the propoxyphene group was detoxified from methadone approximately twice as rapidly. In addition, they were better able to hold jobs and they reported fewer physical complaints during detoxification.

Cases of propoxyphene hydrochloride (PCl) abuse and true physical addition,[13-20] along with many cases of PCl overdose and death,[21-26] have been reported in the medical literature in recent years. The potentially lethal consequences of propoxyphene overdose, with intoxification frequently complicated by pulmonary edema, convulsions† and generalized central nervous system depression,[22] warrants further elucidation here as regards the water solubility of its two common clinical salts. Propoxyphene napsylate is only slightly soluble in water (1.5 mg per ml), whereas PCl is highly soluble in water (2 gms per ml).[27] It follows, then, that because of this crucial distinction in water solubility, PN may well have a lower overdose potential than PCl. Indeed, a 9 gram dosage of PN has been survived without sequelae.[1,2]

Methods

A pilot study, suggested by the research of Tennant,[1,15] Bergin and List (unpublished data), was begun in August, 1973, to study outpatient detoxification of heroin addicts with the use of PN. Volunteer patients from the Drug Detoxification, Rehabilitation, and Aftercare Project of the Haight-Ashbury Free Medical Clinics were selected for the study.

The clinic has used PCl in prescribed therapeutic analgesic dosages since it became clinically available, as a part of its symptomatic therapy for opiate withdrawal;[28] but it had never before employed PN either in large (600 to 1,400 mg per day) dosages or as the sole drug in the management of heroin withdrawal symptoms.

Thirty-two patients were selected. The basis for admission to the PN program was a demonstrated,

*Unpublished data, see Addendum to References

†Convulsions appear to be particularly common with propoxyphene overdose, much less frequent with other opiate and opioid drugs.

continued refractiveness to other available treatment approaches and documented frequent recidivism into heroin or multiple-drug abuse.

Each patient selected was interviewed informally in a non-punitive fashion, and was encouraged to freely state any opinions or observed subjective effects of PN therapy.

PN was administered to each client twice a day. The first of these daily doses could therefore be administered to the patient while he was under the direct observation of the clinic staff. In this manner, the responses to PN doses were observed and evaluated daily for a few hours post ingestion. A second dose of PN was determined from these evaluations. The second dose was then given to each patient to be taken at home.

The only other drugs administered to these patients during the study period were either chloral hydrate or flurazepam (Dalmane®). These were dispensed for sleep during the initial three to four days of acute opioid detoxification.

Results

Of the 32 subjects chosen for this program, 22 (69 percent) were male and ten (31 percent) female. The age range was typical of that of all clinic patients, with 6 percent less than 21, 38 percent between 21 and 25, 34 percent between 25 and 30, and 22 percent over 30 years old. Twenty-eight (88 percent) were Caucasian, three were Black and one was Asian. Inquiry into the length of time since first addiction disclosed that two (6 percent) had been addicted for more than ten years, nine (29 percent) had been first addicted between five and ten years ago, eleven (35 percent) between three and five years ago, five (16 percent) between two and three years ago, and four persons (13 percent) had first developed a heroin habit less than two years ago. Six of the patients (20 percent) reported "light" habits ($20 per day or less), while ten (33 percent) described "heavy" habits ($50 per day or more); the remainder were in the "moderate" habit range ($20 per day to $50 per day).

Many of the patients in the PN program had been seen for some length of time at the clinic. Fully one-third of the total sample had been to the clinic more than 50 times by the beginning of November, 1973. This is important because the PN sample may be biased in favor of long-term addicts who have had many relapses and therefore may represent something of a hard core.

The duration of therapy with PN extended from one to sixty-six days, with the majority of patients, 19 (69 percent) being seen for periods of five to thirty days. PN dosages for acute opiate withdrawal symptoms ranged from 600 mg to 1,400 mg per day.

TABLE 1.—*Results of Urinalysis in PN Program*

	Specimens	*Percent*
Total urine specimens received	182	
Patients refusing to give urine specimen	12	7
Total negative results for drugs	6	3
Positive results for drugs:		
Propoxyphene	137	75
Phenobarbital	43	24
Any illicit drug	53	29
Morphine	34	19
Codeine	13	7
Methadone	6	3
Amphetamine	5	3
Barbiturate	2	1
Cocaine	0	

Two methods of evaluating the success of the PN program were used: urinalysis and counselor evaluation. Results of urinalysis are shown in Table 1.

The patients seemed to be taking the PN much as scheduled and were not submitting someone else's urine. The urine was significantly freer from drugs than that of patients not in the PN program (29 percent of urine specimens tested positive for drugs as opposed to 39 percent for clinic patients generally during 1973). Abuse of amphetamines and barbiturates appeared especially low.

Subjective Data from Patients in PN Program

Reports of Heroin Blockage

Seventeen patients acknowledged concurrent use of heroin after taking PN. Seven of these (41 percent) reported no interference or block of heroin effects. Seven (41 percent) reported a partial block and one reported a total blockage of effects. Two patients reported a slight potentiation of heroin effects.

Reports of Decreased Libido During PN Therapy

Three patients reported a decreased libido not noticed before beginning PN therapy. Two patients reported a decreased libido, but admitted to noticing it before starting PN therapy (probably resulting from heroin and opiate abuse). One patient experienced an increase in libido when doses of PN were decreased. The remaining patients made no comment in this regard.

TABLE 2.—*Frequency of Side Effects Reported by Patients Taking PN*

Feeling of detachment, a psychotogenic drug-like reaction	4
Dizziness	1
Drowsiness	2
Nervous and "Jittery" after PN ingestion	2
"Shaky" before each morning dose of PN	2
Headaches	2
Morning "Hangover"	1
Blurred vision	1
"Metallic" or "Funny Darvon-N" taste	2
"Darvon-N Smell" to everything	1
"Tingling" numbness of teeth, gums, or mouth	2
Leg and joint cramps	1
Upset stomach	2
Constipation	2
Emesis	1

TABLE 3.—*Withdrawal Symptoms Reported in PN Program*

Symptoms	*Days of Therapy*
Severe heroin-like withdrawal symptoms from abrupt termination of PN	33
Mild heroin-like withdrawal symptoms on abrupt termination of PN	30
Same as above	40
Increased anxiety noted from a quick 5-day tapering of PN	39
Increased anxiety and nervousness from abrupt termination of PN	10
Chills, shakes, aches and pains of low intensity from abrupt termination of PN	16

Opioid Withdrawal Symptoms Suppressed by PN

Ten patients (31 percent) reported no withdrawal symptoms while taking PN, as opposed to only three (9 percent) who reported that it did not help. Nineteen patients (59 percent) reported almost total suppression of symptoms. Fifteen (47 percent) reported insomnia which persisted for the first three days but improved on or about the fifth day (Tennant's[1,15] and Bergin's [unpublished] data support this). Consistently, the usual requests for additional medications (sedatives, tranquilizers and anticholinergics) diminished significantly between the third and fifth days. The patients often stated that they felt much better at that time and that Darvon N was working. Ninety-one percent claimed a decreased heroin "yen" while taking PN.

Report of Side Effects

Twelve patients (38 percent) reported no side effects and eleven (34 percent) reported some side effects. In only two cases were side effects (emesis and blurred vision) severe enough to cause the termination of therapy. The side effects and frequency of reports are shown in Table 2.

Report of Propoxyphene Withdrawal Symptoms Precipitated by Tapering or by Termination of PN

Six patients (19 percent) reported no withdrawal symptoms upon termination of dosage. Twenty patients offered no comments or were unavailable to follow-up. Six patients (19 percent) reported withdrawal symptoms (Table 3).

Interaction with Other Abused Drugs

Codeine was the most frequent concurrently abused drug; this was confirmed by urinalysis (7 percent of all urine specimens collected). Also noted were methadone (3 percent), amphetamines (3 percent) and pentobarbital (1 percent). Some patients alleged concurrent abuse of methaqualone (2 percent) as well. The program intermittently dispensed phenobarbital, chloral hydrate, flurazepam and diazepam for sleep. No interaction with any of these drugs was reported. Three patients alleged a potentiation effect of alcohol when taken in combination with PN.

Propoxyphene Mood Changes

Nine (28 percent) patients noted pleasant euphoria after taking PN and one noted dysphoria. In addition, nine patients reported a "drugged" feeling within one hour after oral ingestion of PN (usually with the higher dosages dispensed). Pinpoint pupils, some slurring of speech and a definite "drugged state" were observed in some cases. Sleep patterns were noted to improve and "even out" after the third to fifth days.

Diversion

One case of diversion of PN to outside "street" use noted. (Tennant reports this is a common practice in his population.)

Hepatitis

Two cases of hepatitis, as determined by liver profile, were observed in the study population. Clinically, these were probably not related to PN therapy.

Discussion

Though compromised by the lack of absolute control in an outpatient population, this pilot study nonetheless clearly delineates a number of important clinical considerations. PN is felt to possess some of the disadvantages of methadone,

and yet appears to have some significant advantages. From the data accumulated, it is felt that PN may be viewed as a promising therapeutic adjunct to opiates in the management of physical dependence. However, a long term program of detoxification probably would be best suited to the hard-core, multi-relapse population studied. It is felt that this longer treatment period would enable the patient to develop a fuller counselor relationship and would provide adequate time for voluntary entrance into socio-vocational rehabilitation programs before termination of medication. As ever, total abstinence from drugs by any drug-abusing individual is a multi-disciplinary problem, and one not to be easily dismissed as remedial by purely pharmacotherapeutic methods. The patients in this study who responded best to PN therapy were repeatedly noted to have established a much "tighter" counselor relationship than those who responded poorly.

A clinically observed improvement in the subjective effects of PN (including alterations in mood) during the third to fifth days of therapy was noted in our study population and was also observed by Tennant[1,15] and Bergin (unpublished data). This may prove to be a very significant observation in view of the current hypothesis that the inhibition of the heroin abstinence syndrome of PN is, in fact, due to its unconjugated metabolites, nor-propoxyphene and bi-nor-propoxyphene. Studies by McMahon, et al[29] have shown the presence of one major propoxyphene metabolite in humans: nor-propoxyphene. It was also observed that the concentration of nor-propoxyphene in human plasma was much higher than that of propoxyphene itself and that it had a substantially longer biological half-life. McMahon further suggests that nor- and bi-nor-propoxyphene attain measurable plasma concentrations 75 hours after oral administration of propoxyphene. Thus, a possible correlation between clinical data and the proposed active metabolite hypothesis is reported.

Significant findings of this pilot project included:

- An almost universal acceptance that "PN works" by the group studied.
- PN suppresses the symptoms of opiate withdrawal and, in sufficient dosage, significantly diminishes the "yen" of heroin craving.
- PN is effective in a single or in a divided (twice a day) oral dose.
- A stabilization of mood and affect appears after three to seven days, along with improved sleep patterns.
- Although PN is capable of producing habituation and physical dependence, the withdrawal phenomena of PN are less than those produced by either heroin or methadone.
- Acute or chronic toxicity does not appear to be a significant factor in the dosage employed.

Our results suggest three areas for clinical study using PN in the management of heroin or methadone dependence:

1. *Heroin Detoxification*

(a) Five-day therapy with multiple low daily PN dosages.

(b) Twenty-one-day inpatient or outpatient therapy with PN administered once or twice daily.

(c) Long-term outpatient detoxification of one to six months duration with PN given once or twice daily.

2. *PN Maintenance*

3. *Methadone Detoxification*

(a) Graduated supplementation with PN correlated with decreasing methadone dosage, followed by a graduated decrement of PN.

(b) Abrupt substitution of PN for methadone, followed by graduated decrement of PN.

The current limiting factors of PN therapy have to do with acute and chronic toxicity. Mindful of the severe consequences of acute propoxyphene toxicity, a divided dosage regime is suggested, allowing for some drug-symptom observation in addition to a greater safety margin.

Kiplinger et al[30] have reported ten cases of anicteric hepatitis (probably not related to drug use) in a study population of prison inmates administered PN and PCl salts chronically for six months. Also, liver enlargement, fatty liver changes and increased serum liver enzymes have been previously noted in rats and dogs treated for short terms with high doses of hydrochloride and napsylate propoxyphene salts.[31]

Further research and full assessment of the biopharmaceutical and pharmacokinetic properties involved with absorption of PN from the human gastrointestinal tract must be undertaken. Future double-blind human studies and controlled protocol are obviously needed to establish safe standards, especially in regard to PN dosage. Clearly, PN shows great promise in detoxification or mainte-

nance substitution therapy for opiate and opioid dependence. What is needed now is a clinical and laboratory examination that is deliberate, thorough and highly disciplined.

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Addendum:

Unpublished data reported in this study were drawn from the following:

1. Bergin D: Caseload statistic summary of Darvon-N detoxification. Unpublished data from The Aquarian Effort, 2104 Capitol Avenue, Sacramento, California, Nov 13, 1973;

2. List N, Craig R, Athanesiou R: The use of propoxyphene in long term detoxification in patients on methadone. Unpublished data from Glenwood Life Center, Baltimore, Maryland, Nov 1973.