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Noradrenergic Role in the Self-Administration of Ethanol[1]

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DAVIS, W. M., S. G. SMITH AND T. E. WERNER. *Noradrenergic role in the self-administration of ethanol.* PHARMAC. BIOCHEM. BEHAV. 9(3) 369–374, 1978.—Involvement of noradrenergic and/or dopaminergic processes of the brain in self-administration behavior toward ethanol was assessed in rats allowed to lever-press for 25 mg/kg intragastric doses on a CRF schedule. Initial access to infusions of saline for establishing an operant baseline was followed by one 10-hr session on acquisition contingencies for ethanol and then one extinction session on saline. Prior to a reacquisition session, rats were treated with either (a) saline, (b) alpha-methyl-p-tyrosine (AMT; 225 mg/kg), (c) 1-phenyl-3-(2-thiazolyl)-2-thiourea (U-14,624; 600 mg/kg or 300 mg/kg), or (d) haloperidol (3.5 mg/kg). Only the saline-pretreated control group and the haloperidol-treated rats reacquired lever-press behavior. Groups treated in like fashion, but pressing for a sweet milk reinforcer, all showed reacquisition. Thus, the effects of AMT and U-14,624 are attributed to an interference with the reinforcing effect of ethanol infusions. Brain levels of norepinephrine were depleted by both compounds, dopamine was depleted only by AMT, and serotonin was elevated by 600 mg/kg of U-14,624 but unaffected by 300 mg/kg. These results suggest that a cerebral noradrenergic system plays an important role in the reinforcing effect of ethanol without an involvement of dopaminergic systems

Ethanol self-administration α-Methyl-p-tyrosine U-14,624 Haloperidol Intragastric self-administration Drug self-administration behavior

THERE has been considerable interest in putative central neurotransmitters which may be involved in the reinforcing effect of ethanol. Various drugs that alter levels of brain serotonin (5-HT) have been reported to reduce the selection of ethanol by rodents. These include 5-hydroxytryptophan [15,19], pargyline [24], *para*-chlorophenylalanine (PCPA) [5, 20, 23] and *para*-chloramphetamine [14]. Pretreatment with α-methyltryosine (AMT), a drug which reduces brain levels of norepinephrine (NE) and dopamine (DA), also has been reported to modify ethanol selection behavior [20].

Often the interpretation of such findings are unclear because the pretreatment drugs may (a) affect more than one neurotransmitter, as do pargyline and AMT, (b) produce confliction results, e.g., PCPA being reported to decrease ethanol selection [20], to have no effect [24], or to increase ethanol selection [15,16], (c) produce aversive or toxic effects that could become conditioned [21], (d) induce muscle weakness or sedation [9], or (e) augment aversive taste factors inherent in oral ethanol.

The present experiments studied possible involvement of central noradrenergic and/or dopaminergic systems in ethanol self-administration behavior, while avoiding certain problems outlined above. The intragastric mode of infusion was used to avoid problems associated with taste of ethanol solutions taken orally. The pharmacological agents employed were tested for ability to block the reinforcing action of not only ethanol, but also sweet milk, a customary appetitive reinforcer. AMT was used as a depleting agent for both NE and DA, whereas 1-phenyl-3-(2-thiazolyl)-2-thiourea (U-14,624) was employed for its capacity to deplete NE but not DA. The appropriateness of the dosage of U-14,624 employed was verified by brain assays for NE, DA and 5-HT.

METHOD

Animals

The animals were 82 experimentally naive, adult male Sprague-Dawley rats weighing 300–350 g at the start of the research. Each was housed in an individual home cage between experimental sessions. Food and water were available continuously in both the home cages and the experimental chambers.

Apparatus

Each rat was implanted with a chronic indwelling intragastric catheter and fitted with an external saddle [28]. The saddle was designed to permit connecting to an infusion system, while producing a minimum of restraint of normal movements. When activated, the infusion system delivered 0.092 ml of 0.9% saline solution, milk or ethanol solution in 1 sec. The experimental chambers each consisted of a clear plastic cylinder 24 cm in height by 25 cm in diameter containing an infusion system, a response lever, food and water, and

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each was enclosed within a vented, sound-attenuated compartment. Programming of contingencies and data recording were by means of electromechanical circuitry. Details of the infusion apparatus, experimental chambers and electrical equipment have been presented [26].

Behavioral Procedure

After a 5-day period for recovery from the stress of surgery, a 7-day training period was conducted to facilitate the acquisition of operant responding for intragastric doses of sweet milk. (Sweetened condensed milk (Eagle Brand) diluted to 1/2 strength with distilled water.) During this time, oral access was given to a quantity of 15 ml each day without food or water deprivation. Additionally, on the last 5 days an intragastric infusion of 5 ml of sweet milk warmed to room temperature was administered by the experimenter. In contrast, it was known from our previous observations [13, 28–30, 32] that rats receiving ethanol required no pretraining to show ready acquisition; therefore, none was used for those animals assigned to the ethanol treatments.

On Day 1 of the experimental procedure, the rats were placed in self-administration chambers and attached to the infusion system for a 1-hr adaptation period. Then during a 10-hr period the operant baseline level was recorded with intragastric infusions of saline solution given for lever-presses on a CRF schedule. Superimposed on the 1-sec infusion interval was a buzzer. On Day 2 a 10-hr acquisition period was given under the same conditions except that either a 25 mg/kg dose of ethanol or a dose of sweet milk was substituted for saline. On Day 3 a 10-hr extinction period was given by substituting saline for ethanol or milk. On Day 4, prior to the 10-hr reacquisition session, control or drug treatments (Table 1) were administered through the intragastric cannula before the rats were given access to the self-administration contingencies of Day 2.

Drugs

All drug and vehicle dosing was conducted by intragastric administration. L-α-methyl-p-tyrosine (Regis Chemical Co., Chicago, IL) was readily suspended in a 0.9% saline solution without a suspending agent by use of a Polytron® homogenizer. U–14,624 (Regis) was suspended in 1% methylcellulose solution. Haloperidol, as the injectable solution (Haldol®, McNeil Labs), and ethanol were diluted with 0.9% saline solution. Control groups received either a 0.9% saline solution or 1% methylcellulose solution, corresponding to the vehicle received by the respective treatment groups. The dosage schedule for AMT was the same as previously [7,8], i.e., 3 doses of 75 mg/kg at 4-hr intervals. The dosage for U–14,624 was one we formerly used [11,12], i.e., 600 mg/kg given 4 hr before the reacquisition session; however, 300 mg/kg was also tested. The dosage of haloperidol, 3.5 mg/kg, was reduced by 30% from one previously used intraperitoneally [11,25] to reduce the possibility of motor impairment. The unit dose per infusion for ethanol (25 mg/kg) was chosen on the basis of previous studies that also used doses as high as 100 mg/kg, in which it was found not to cause deleterious behavioral effects [28–30, 32].

Brain Amine Assays

The levels of NE, DA and 5–HT [22] in the whole brain (minus cerebellum) were determined at 4, 8, 28 and 100 hr after oral doses (in uncannulated rats) of 300 and 600 mg/kg of U–14,624, or equal doses of the vehicle, using at least 3 rats per determination. Because the effects of AMT are well established, and as we have previously reported data from this laboratory [12] such analyses were not repeated.

Statistical Analysis

Results were analyzed by use of one-way analysis of variance and *t* tests (two-tailed) for related or independent measures [4].

RESULTS

AMT, U-14,624 and Haloperidol on Ethanol Self-Administration

Figure 1 shows the effects of AMT on ethanol self-

TABLE 1

PROTOCOL OF TREATMENTS BEFORE REACQUISITION SESSION

Reinforcer	N	Pretreatment Drug	Intragastric Dose	Interval
Experiment 1				
Alcohol	8	AMT	3×75 mg/kg	4-hr; last dose
Alcohol	8	Saline	equal volume	4 hr before session
Alcohol	5	U-14, 624	600 mg/kg	4 hr before
Alcohol	5	Vehicle	equal volume	session
Alcohol	5	U-14, 624	300 mg/kg	
Alcohol	5	Vehicle	equal volume	
Alcohol	5	Haloperidol	3.5 mg/kg	30 min before
Alcohol	5	Saline	equal volume	session
Experiment 2				
Milk	8	AMT	3×75 mg/kg	
Milk	8	Saline	equal volume	
Milk	5	U-14, 624	600 mg/kg	same as
Milk	5	Vehicle	equal volume	Exp. 1
Milk	5	U-14, 624	300 mg/kg	
Milk	5	Vehicle	equal volume	

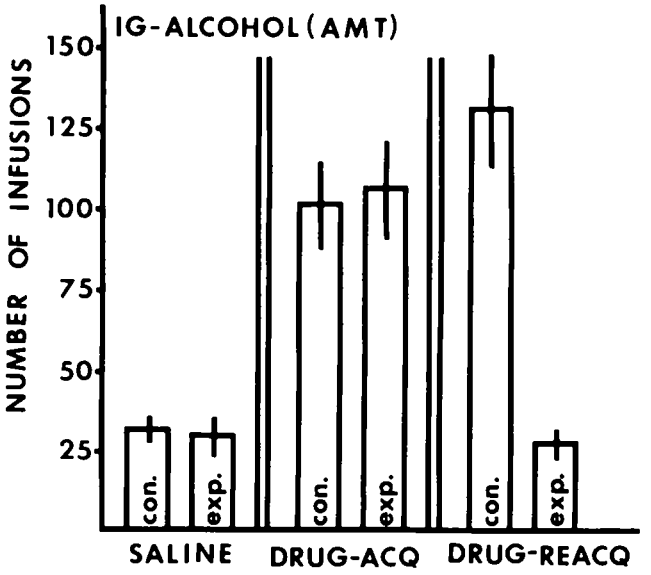

FIG. 1. Effect of α-methyltyrosine (AMT) on intragastric self-administration of alcohol by rats. Dosage of alcohol delivered for each lever-press during 10-hr acquisition (ACQ) and reacquisition (REACQ) sessions was 25 mg/kg. The experimental (exp.) group received 225 mg/kg of AMT prior to REACQ session in 3 divided doses, while the control (con.) group received saline. Data are shown as mean (and SEM) number of infusions for groups of 8 rats.

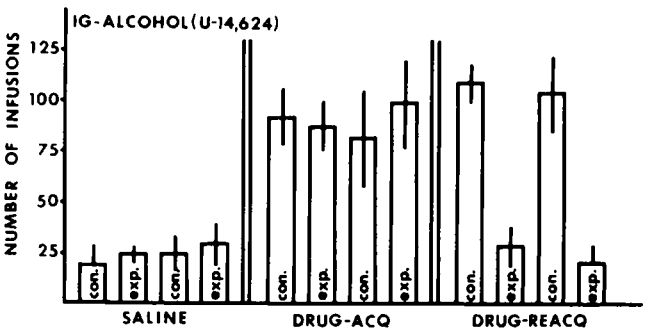

FIG. 2. Effect of U-14,624 on intragastric self-administration of alcohol by rats. Dosage of alcohol delivered for each lever-press during 10-hr acquisition (ACQ) and reacquisition (REACQ) sessions was 25 mg/kg. The experimental (exp.) groups received a dose of either 300 mg/kg (left) or 600 mg/kg (right) of U-14,624 prior to REACQ session, while the control (con.) groups received an equal volume of vehicle for U-14,624. Data are shown as mean (and SEM) number of infusions for groups of 5 rats.

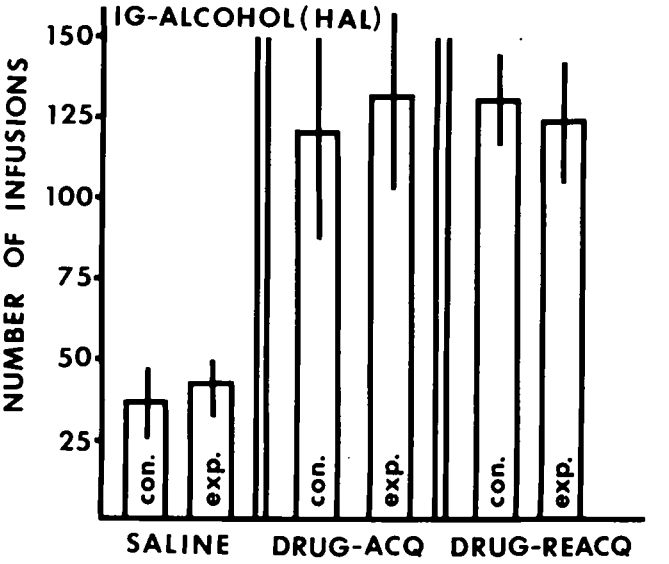

FIG. 3. Effect of haloperidol on intragastric self-administration of alcohol by rats. Dosage of alcohol delivered for each lever-press during 10-hr acquisition (ACQ) and reacquisition (REACQ) sessions was 25 mg/kg. The experimental (exp.) group received 3.5 mg/kg of haloperidol i.g. at 30 min before the REACQ session, while the control (con.) group received saline. Data are shown as mean (and SEM) number of infusions for groups of 5 rats.

administration behavior. Experimental and control groups did not differ during operant level and acquisition sessions ($p>0.05$). However, a difference was observed during reacquisition, the AMT-treated group responding significantly less than did the saline pretreated group ($p<0.01$). Comparisons between the operant level and reacquisition responding showed a significant increase for the saline-treated group ($p<0.001$), but no change for the AMT-treated group ($p>0.05$). This indicates that ethanol self-administration behavior was blocked by AMT, but that responding was not suppressed below the initial baseline levels.

Effects of U-14,624 on ethanol self-administration behavior are shown in Fig. 2. Whereas no difference was seen between experimental and control groups for operant level or acquisition sessions ($p>0.05$), the responding in reacquisition of both 300 and 600 mg/kg U-14,624 groups was significantly reduced ($p<0.01$) from that of the vehicle control group. Comparisons between their operant level and reacquisition responses showed a significant increase for the vehicle group ($p<0.001$), but no change for either U-14,624 group ($p>0.05$). These data indicate that U-14,624 blocked self-administration of ethanol without suppressing behavior below the initial operant baseline.

The effects of haloperidol on self-administration of ethanol are shown in Fig. 3. No difference was found between experimental or control groups for either the operant level, acquisition or reacquisition sessions ($p>0.05$). Thus, the data indicate that haloperidol had no effect on ethanol self-administration behavior.

AMT and U-14,624 on Responding for Sweet Milk

The effects of AMT on lever pressing behavior for sweet milk are shown in Fig. 4. The numbers of infusions taken by each group indicate that no significant difference occurred between the experimental and control groups during either operant level or acquisition sessions and during reacquisition following pretreatment with AMT or saline. These data indicate that AMT did not produce any toxic or aversive effects that could decrease self-administration of sweet milk, nor did it reduce the effectiveness of sweet milk as a reinforcer.

The effects of 300 or 600 mg/kg of U-14,624 on self-administration of sweet milk are shown in Fig. 5. Comparisons show that operant level, acquisition, and reacquisition

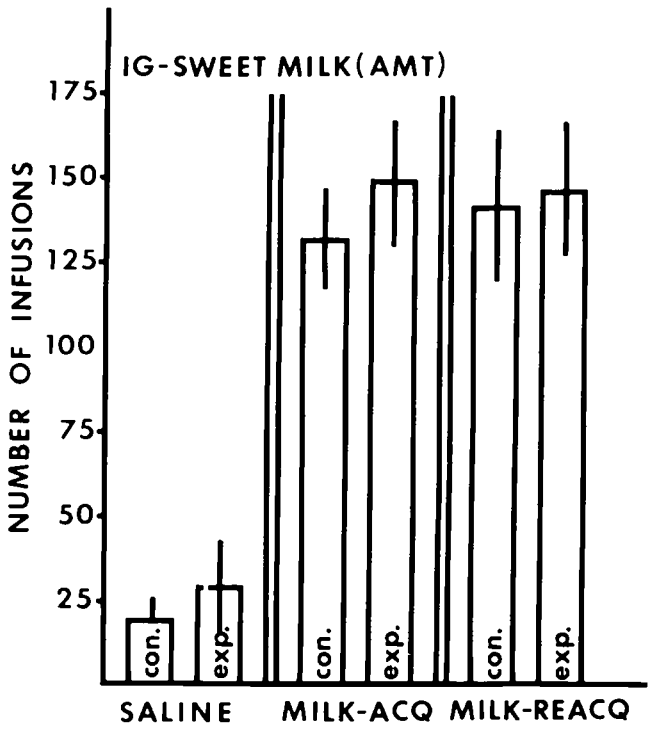

FIG. 4. Effect of α-methyltyrosine (AMT) on intragastric self-administration of sweet milk by rats. Lever-press responses reinforced by delivery of milk during a 10-hr acquisition (ACQ) session are compared to responses when only saline was delivered. Data shown are mean (and SEM) number of infusions for groups of 8 rats. Prior to the reacquisition (REACQ) session, following an extinction session, the experimental (exp.) group received 225 mg/kg of AMT (divided in 3 doses), while the control (con.) group received an equal volume of saline.

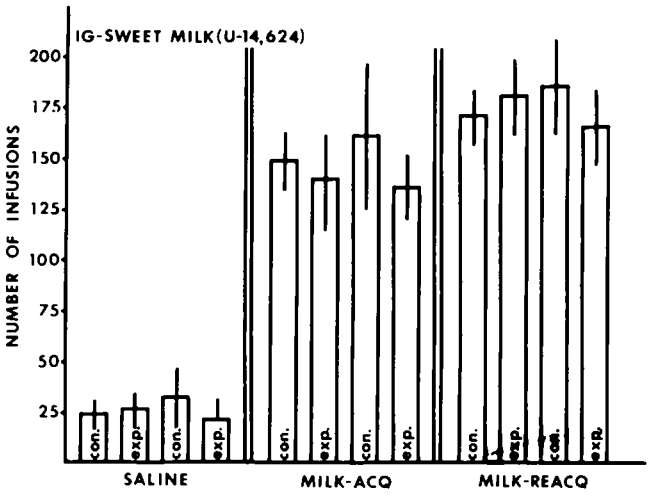

FIG. 5. Effect of U-14,624 on intragastric self-administration of sweet milk by rats. The experimental (exp.) groups received a dose of 300 mg/kg (left) or 600 mg/kg (right) of U-14,624 prior to REACQ session, while the control (con.) groups received an equal volume of vehicle for U-14,624. Data are shown as mean (and SEM) number of infusions for groups of 5 rats.

responding did not differ significantly ($p>0.05$) between U-14,624 and vehicle groups. Thus, both doses of U-14,624 did not produce toxic or aversive affects that could inhibit self-administration of sweet milk, nor did they reduce its reinforcing effect.

U-14,624 on Brain Amines

The results of brain amine assays for NE, DA and 5-HT following 300 and 600 mg/kg of U-14,624 are shown in Tables 2 and 3. After the 600 mg/kg dose, NE was significantly reduced and both DA and 5-HT were elevated. The 300 mg/kg dose of U-15,624 also depleted NE and slightly increased DA, but it had no effect on 5-HT.

DISCUSSION

Behavioral data of this study show that reacquisition of self-administration behavior for ethanol by rats was prevented by both AMT and U-14,624, but not by haloperidol. As the former two agents both reduce the synthesis of brain NE, but are opposite in their effects on DA levels, and because haloperidol is an effective blocker of central DA receptors, it does not appear likely that DA could have been involved in the failure of self-administration. The neurochemical data suggested that any of the three maines, NE, DA and 5-HT, could have been involved in effects seen with the 600 mg/kg dose of U-14,624, but with only depletion of NE occurring as a likely basis for effects of the 300 mg/kg dose. This point is further supported by research showing that ethanol infusion reduces brain NE levels, whereas DA levels are unaffected [6,17]. The lack of effect of haloperidol is in contrast to its interference with reinforcement associated with intravenous doses of d-amphetamine [27].

The possible involvement of 5-HT in these effects should

TABLE 2

NE, DA AND 5-HT LEVELS FOLLWING A SINGLE DOSE (300 MG/KG, P.O.) OF U-14, 624 IN RATS

Time (hr) Post-Drug	NE		DA		5-HT	
	Saline	U-14, 624	Saline	U-14, 624	Saline	U-14, 624
4	0.281 ± 0.003*	0.149 ± 0.005†	0.951 ± 0.025	1.035 ± 0.040	0.452 ± 0.007	0.444 ± 0.015
8	0.308 ± 0.012	0.111 ± 0.004‡	0.892 ± 0.018	1.019 ± 0.033†	0.462 ± 0.014	0.434 ± 0.010
28	0.305 ± 0.010	0.102 ± 0.015‡	0.926 ± 0.029	0.994 ± 0.035	0.458 ± 0.017	0.480 ± 0.019
100	0.279 ± 0.012	0.268 ± 0.008	0.925 ± 0.027	0.929 ± 0.015	0.457 ± 0.007	0.455 ± 0.021

* Each value (μg/g) is a mean ± SEM of at least 4 rats.

† or ‡ Significantly different from its corresponding saline controls at $p<0.05$ or 0.001, respectively, by two-tailed t test.

TABLE 3

NA, DA AND 5-HT LEVELS FOLLOWING A SINGLE DOSE (600 MG/KG, P.O.) OF U-14, 624 IN RATS

Time (Hr) Post-Drug	NE		DA		5-HT	
	Saline	U-14, 624	Saline	U-14, 624	Saline	U-14, 624
4	0.391 ± 0.024*	0.183 ± 0.005‡	0.895 ± 0.021	0.869 ± 0.014	0.735 ± 0.001	0.791 ± 0.072
8	0.342 ± 0.027	0.059 ± 0.000‡	0.906 ± 0.026	1.030 ± 0.009†	0.713 ± 0.052	1.028 ± 0.105†
28	0.366 ± 0.010	0.120 ± 0.007‡	0.933 ± 0.020	0.926 ± 0.030	0.781 ± 0.052	0.969 ± 0.023†
100	0.374 ± 0.013	0.186 ± 0.079‡	0.985 ± 0.035	0.947 ± 0.034	0.946 ± 0.050	0.924 ± 0.034

* Each value (μg/g) is a mean ± SEM of at least 3 rats.

† or ‡ Significantly different from its corresponding saline controls at $p<0.05$ or 0.01, respectively, by two-tailed t test.

also be considered in light of previous reports [5,19] of its relationship to ethanol selection. U–14,624 has been found to elevate brain 5–HT in certain doses [18], as we also did in this case with the 600 mg/kg dose. (While the brain amine determinations were made in unoperated rats, we believe extrapolation of their results to the cannulated rats is valid in light of the extensive (>8 days) period after surgery before the chemical manipulation of brain amines in the latter animals.) However, the lack of effect on 5–HT for the 300 mg/kg dose of U–14,624 while still causing a reduction of NE level, makes it unlikely that the effects of U–14,624 on ethanol self-administration behavior involved brain 5–HT. In the case of AMT, it is known that NE and DA levels are reduced as a result of its inhibition of tyrosine hydroxylase, without any concurrent change in brain 5–HT [31].

Thus, the data reported here suggest that noradrenergic brain mechanisms are responsible for the effects of AMT and U–14,624 on self-administration behavior for ethanol. The same inference has been drawn by others from data showing suppresion of oral ethanol intake in rats after disulfiram [2], FLA–63 [2] or FLA–57 [1,3]. These agents all act similarly to U–14,624 as inhibitors of dopamine β-hydroxylase, reducing brain NE but not DA. Thus, despite considerable methodological differences, the present study and previous ones [1–3] are quite complementary.

The behavioral effects reported here are not attributable to motor disability or other non-specific depressant actions because lever-pressing was not abolished or reduced below the initial operant baseline level. That there was not a complete elimination of appetitive responding by the treatments that blocked reacquisition of ethanol self-administration is clearly shown by the rats' responding for sweet milk under the same conditions. Thus, the controls in these experiments are such as to permit the conclusion that the drug effects on self-administration behavior represent a particular interference with the reinforcing properties of ethanol in the rat.

These findings for ethanol are parallel to earlier results with both morphine and *d*-amphetamine in the same test situation after either AMT or U–14,624 [7, 8, 12]. Assuming that the basis for reinforcement associated with ethanol self-administration is similar in rats and in human beings, then treatment of human users of ethanol with an agent acting like AMT or U–14,624 toward noradrenergic functions, but lacking significant toxicity, should hinder or prevent the primary pharmacological reinforcing actions that provide strong motivation toward abuse of ethanol. Consequently, such an agent might be applicable for therapeutic procedures designed to extinguish the conditioning that establishes drug abuse behaviors [3,10]. An added significance of such treatment might be derived from the likely capability of acting against each of three prototypic abuse agents—ethanol, amphetamine, and morphine—or their surrogates.

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