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Original Articles

Acute Psychosis Induced by Psychotomimetic Drug Abuse

I. Clinical Findings

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Twelve patients with acute drug-induced psychotic reactions were compared on a variety of clinical measures to 26 patients with acute psychotic reactions unrelated to drug abuse. The drug-induced patients tended to score prospectively higher on a number of items which have been shown to have predictive value for prognosis in psychotic states. The drug-induced patients appeared clinically similar to patients with "good premorbid" or "schizophreniform" psychotic reactions.

The recent phenomenon of psychotomimetic drug abuse has led to a number of noteworthy clinical phenomena including the production of prolonged acute psychotic states. Controversy has arisen over the nature of these states. Are they clearly different from naturally occurring psychotic states? Are they psychotic reactions "triggered" in "prepsychotic" individuals or do they represent some kind of psychotic state *sui generis*? Using a number of clinical and neurochemical parameters we have compared a group of psychotic reactions, where the onset seemed intimately temporally related to ingestion of a psychotomimetic substance, with a group of acute psychotic reactions where no history of drug use was obtained. This paper reports the clinical findings.

Methods

All patients had been hospitalized for treatment of an acute psychotic disorder. None of the 12 patients (seven males and five females) which comprised the drug group had been hospitalized previously for psychiatric illness. In each instance drug ingestion had led to the production of an acute psychotic reaction which ultimately required hospitalization and (in every case except one) phenothiazine treatment. The drug experience which resulted in the prolonged psychotic state took place from two to seven days prior to hospital admission. Six patients had allegedly taken D-lysergic acid diethylamide (LSD), four had used mescaline, and two amphetamines. Since "mescaline" obtained illicitly has frequently been shown to be LSD by chemical analysis,[1] the majority of our subjects were probably LSD abusers. Three of the 12 patients claimed to have taken psychotomimetics extensively, eg, more than ten other times. The other nine had used these substances less than three times previously. No prior ingestion had led to a psychopathological state greater than 24 hours in duration. Most of the drug group had used marihuana extensively. The control group consisted of 26 patients (ten men and 16 women) who suffered acute psychotic reactions apparently unrelated to drug use, which required treatment with phenothiazine compounds. Six of the controls had been hospitalized previously for psychotic reactions. One control patient had allegedly taken LSD once eight months prior to his becoming psychotic but apparently had functioned reasonably well in the interim. Two control patients had used marihuana occasionally though no recent use seemed related to the onset of psychotic symptoms. Otherwise no history of illicit drug use was obtained from the control group.

Acute symptoms were scored by means of the Brief Psychiatric Rating Scale (BPRS). The following additional clinical ratings were performed (Table 1). Adolescent social adjustment,[2] intelligence,[3] and bizarreness of delusions[4] were rated by means of a 3-point scale with greatest impairment receiving the highest scores. The Stephens-Astrup prognosis form was scored using a 3-point scale with the prognostically more favorable ratings receiving the highest scores.[5] Each patient was rated positive or negative depending upon the presence or absence of Schneider's first-rank symptoms.[6,7] The category delusional percept was excluded as a first-rank symptom since our experience suggests that this item is ubiquitous in many acute psychotic states and does not have the discriminating power of the other criteria. Each of the items rated has been reported to be a correlate of severity or prognosis in psychotic states. The two groups were also compared for the frequency of psychiatric illness requiring hospitalization in their families of origin, defined as including parents, siblings, and maternal or paternal siblings. Mean length of stay in the hospital and mean maintenance phenothiazine dose at discharge were calculated for each group. The drug doses were converted to equivalent doses of chlorpromazine for purposes of comparison. All ratings except the BPRS were performed by concensus between two staff psychiatrists who conducted the treatment program.

The mean scores for the two patient groups on each of the rated items were compared by means of a *t*-test (two-tailed). The Schneider ratings on the two groups were compared by a χ^2 test with Yates correction.

Results

Table 2 shows the pretreatment BPRS items which differentiated the two groups of psychotic reactions. Com-

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Table 1.—Clinical Data For Psychotic States

Age
Adolescence
Definitely not socially isolated
Intermediate
Definitely socially isolated
Delusions
Predominately erroneous interpretation of objects or events, minimal bizarre or fantastic ideas
Intermediate
Large amount infantile, fantastic, or bizarre ideas
Stephens-Astrup scale (1, absence of trait; 2, intermediate; 3, presence of trait)
Six months or less from onset to full-blown psychosis
Clear precipitating factors
Married
Good premorbid social adjustment and work history
Presence of depressive features
Personality not schizoid
Guilt feelings expressed
Presence of confusion
Intelligence average or above
Absence of marked emotional blunting
No psychosis in blood relatives
Total score
Schneider first-rank symptoms (rated positive if any category of symptoms present)
Experiences of psychic alienation
Experiences of psychic influence
Complete auditory hallucinations

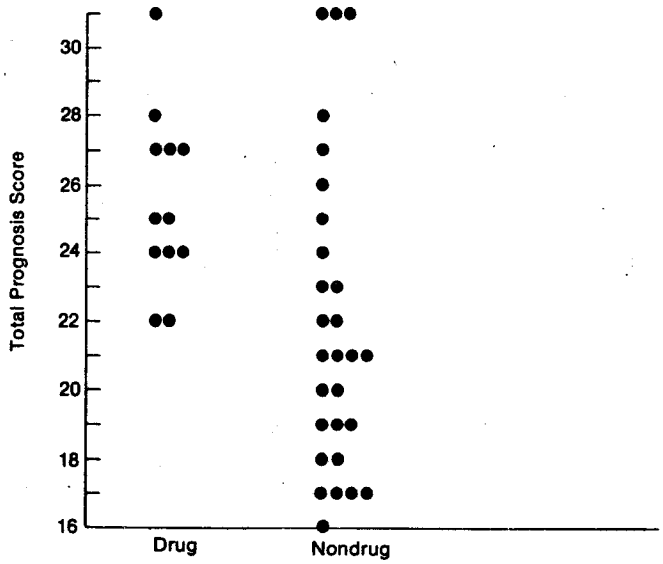
Table 2.—Pretreatment BPRS Items Which Significantly Differentiated Patients With Drug-Induced and Nondrug-Induced Psychotic Reactions

	BPRS Items				
Group	Conceptual Disorganization	Motor Retardation	Blunt Affect	Excitement	Lack of Energy
Drug group					
Mean	4.0	2.81	2.36	3.90	1.72
SD	1.41	1.25	1.20	1.70	0.90
SEM	0.42	0.37	0.36	0.51	0.27
N	11	11	11	11	11
Nondrug group					
Mean	2.56	3.80	3.68	2.36	2.64
SD	1.80	1.22	1.24	1.60	0.99
SEM	0.36	0.24	0.24	0.32	0.19
N	25	25	25	25	25
t	−2.34	2.22	2.97	−2.61	2.63
P	<.05	<.05	<.01	<.02	<.02

pared to the nondrug group, the drug group on admission showed more conceptual disorganization, less motor retardation, less blunted affect, more excitement, and less lack of energy. Table 3 compares the means for the other clinical items. The drug group scored higher in adolescent socialization and with regard to prognostic items on the Stephens-Astrup scale, this group had a briefer onset, clearer precipitants, was married less, was more intelligent, had a better premorbid social and work record, and was less schizoid. The mean total prognostic score was significantly higher for the drug group. The Figure shows the distribution of total prognosis scores for the drug and nondrug group. The drug group is generally clustered

Table 3.—Scores on

Group	Age	Adolescence	Delusions	Onset
Drug group				
Mean	20.3	1.8	2.2	2.7
SD	4.0	0.8	0.7	0.6
SEM	1.1	0.2	0.2	0.1
N	12	12	12	12
Nondrug group				
Mean	23.6	2.4	1.9	2.0
SD	6.2	0.6	0.8	0.8
SEM	1.3	0.1	0.1	0.1
N	22	20	22	22
t	1.65	2.41	−1.09	−2.64
P	NS	<.05	NS	<.02



Distribution of total prognosis scores (Stephens-Astrup) in patients with drug-induced and nondrug-induced psychotic reactions.

above the bulk of the control group. In the drug group three of 12 patients showed the first-rank criteria of Schneider compared to 14 of 26 in the nondrug group. This difference was not significant, however, by χ^2. The Schneider positive, as compared to the Schneider negative nondrug patients had significantly lower mean total scores on Stephens-Astrup prognosis scale ($P < .001$). In the drug group 33% of the patients gave positive family histories (as defined previously) compared to 29% in the control group. The mean maintenance equivalent phenothiazine dose at discharge was 580 mg and 540 mg in the drug and nondrug groups, respectively. The average length of hospital stay was 111 days for the nondrug group compared to 77 days for the drug group. These differences were not significant due to a wide variation in the individual values.

Comment

In the history of the comparative psychopathology of the acute behavioral reaction to psychotomimetic drugs there has been marked disagreement as to whether or not this syndrome was a "model psychosis."[5] Some of the prob-

Clinical Items for Patients With Drug-Induced and Nondrug-Induced Psychotic Reactions

Precipitating Factors	Married	Premorbid Adjustment	Depression	Nonschizoid	Guilt	Confusion	Intelligence	Blunting	Family	Total	Schneider
											3 of 12 positive
2.9	1.1	2.2	2.1	2.0	2.1	2.3	2.9	2.0	2.6	25.5	
0.2	0.5	0.4	0.8	0.9	0.8	0.6	0.2	0.9	0.6	2.6	
0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.2	0.1	0.7	
12	12	12	12	12	12	12	12	12	12	12	
											14 of 26 positive
2.2	1.7	1.7	2.3	1.3	2.1	1.9	2.3	1.5	2.2	21.5	
0.7	0.9	0.7	0.7	0.7	0.8	0.7	0.7	0.8	0.8	4.8	
0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	1.0	
22	22	22	22	22	22	22	22	22	22	22	
−3.30	2.12	−2.27	0.75	−2.51	0	−1.67	−2.89	−1.66	−1.51	−2.66	
<.005	<.05	<.05	NS	<.02	NS	NS	<.01	NS	NS	<.02	

lems and ambiguities with this kind of question have been discussed.[9,10] It was, at best, unwieldy to compare an acute drug response to a chronic behavioral pattern. Hollister's assertion that it is unlikely that one could produce a chronic psychosis by most known chemical agents[8] seems quite untenable today. Experience with casualties from the psychedelic drug scene has established the fact that the illicit drugs of more recent choice (LSD, mescaline, psilocybin) can by single or repeated administration lead to a syndrome which behaves much like nondrug-induced psychosis in the long as well as the short run.[11-15] This study takes a closer look at the clinical picture in this kind of drug-induced psychotic reaction and examines its relationship to nondrug-induced psychotic states.

The clinical data as a whole suggest that the drug-induced psychotic reaction as defined in this report differs in a number of respects from the nondrug-induced psychotic states. Most of these differentiating features point in the direction of more favorable prognostic findings in the drug-induced states. In fact the clinical picture fits that of "good premorbid," "reactive," or "schizophreniform" psychoses quite closely. Better prognostic scores, less affective blunting, and fewer Schneider positive cases are consistent with this similarity.[7,16]

Investigators and clinicians have suggested that prolonged psychotic reactions following psychotomimetic drug use occur only in individuals who are "prepsychotic" or in some way ultimately destined to become psychotic. This judgment is essentially always made retrospectively and, in our hands at least, is a very unreliable one, fraught with possibilities for bias as a result of the psychotic episode itself. Nevertheless, granting such a possibility, one might reason that such a group of patients would be, in some way, most vulnerable to psychosis. Vulnerability to a psychotic state may be something quite separate from prognosis, although it is usually by a retrospective assessment of premorbid function that the judgment of prepsychotic is made. One might thus expect that such a group of individuals would receive low scores on the various prognostic items which have been shown to have some validity for predicting outcome in psychotic syndromes. Such was not the case in this study, however. On five out of 11 Stephens-Astrup items and on the total prognosis score, the drug group measured significantly higher, while on one (marriage) this group scored lower than the controls. We emphasize that we cannot be certain that the prognostic factors are valid for the drug group since follow-up data on the population have not been obtained. The relative absence in the drug group of individuals with very poor premorbid histories may be related to the finding in some populations that social activity parallels drug use.[17,18] On the other hand, it may be that vulnerability to the psychotic altered state of consciousness is a discrete ingredient in the structure of psychotic states, separate from the issue of premorbid personality characteristics and social development. If so, such a concept would be of some importance for the theory and management of psychotic states.

In contrast to schizophreniform or good premorbid states unrelated to drug use, our drug-induced psychotic patients required doses of antipsychotic drugs as great, on the average, as the nondrug group.[7] Further we, in contrast to others,[19,20] found phenothiazines effective in the treatment of the drug-induced states. In summary, our data suggest that the prolonged psychotic reaction precipitated by psychotomimetic drug use closely resembles (prospectively) the good premorbid or schizophreniform psychotic states. Individuals who suffer such reactions tend prospectively to score higher than nondrug psychotic patients on various items related to outcome in psychotic disorders. We do not suggest that the drug-induced states are necessarily more benign. Problems such as suicide and self-mutilation which have been encountered clinically represent a major acute liability in these conditions.[21]

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Acute Psychosis Induced by Psychotomimetic Drug Abuse

II. Neurochemical Findings

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Following probenecid administration lumbar cerebrospinal fluid 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) were measured before and during phenothiazine treatment in 12 patients who developed psychotic episodes following the ingestion of a psychotomimetic drug, probably D-lysergic acid diethylamide (LSD-25) in all but two cases. Compared to nondrug-induced psychotic patients and inmate controls the drug-induced patients gave evidence of decreased central 5HIAA formation, findings analagous to those obtained following the administration of LSD-like drugs to animals. These results persisted during phenothiazine treatment.

In a companion study we have reported some clinical findings in a group of patients with drug-induced psychotic reactions as compared to a group of nondrug-induced psychotic patients. In the present paper we describe certain neurochemical findings in these two groups. We measured lumbar cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA, acid metabolite of 5-hydroxytryptamine or serotonin) and homovanillic acid (HVA, acid metabolite of dopamine) following probenecid administration in both groups. The probenecid procedure has been used as a clinical index of turnover of the parent amines in the central nervous system.[1]

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Methods

The patient populations are described in the preceding paper. Twelve patients with drug-induced psychotic reactions were compared to 26 nondrug-induced psychotic patients. For the drug-induced group, the onset of the psychosis was intimately related to ingestion of a psychotomimetic substance so that the acute drug effect merged imperceptibly with the early symptoms of an acute psychotic reaction. In all cases except two, the drug used was probably D-lysergic acid diethylamide (LSD). All patients in both groups (except one drug-induced patient who received no psychotherapeutic drugs) obtained satisfactory clinical remission by the administration of a single phenothiazine compound, plus antiparkinsonian medication as necessary. These patients would have been grouped in the "schizophrenic spectrum"; borderline syndromes were not included. However, nosological categories have intentionally been replaced by an operational definition of the pa-

Results										
		Before Treatment				During Treatment				
Patient Group		5HIAA*	HVA	5HIAA/HVA	BPRS	Drugs	5HIAA/HVA	HVA	5HIAA	BPRS
Drug-induced psychotics										
	1	67	101	0.61	61	T10	0	0	0	0
	2	5	50	0.10	40		39	90	0.43	22
	3	0	0	0	64	T30,C2	13	88	0.14	36
	4	0	0	0	0	T50,C5	54	180	0.30	55
	5	22	97	0.23	62	T15,C3	24	87	0.28	26
	6	24	89	0.27	54	T40,C3	14	146	0.10	36
	7	0	0	0	57	CPZ600,C2	33	91	0.36	0
	8	28	136	0.21	60	T30,C4	23	160	0.14	26
	9	54	90	0.60	43	T6,C2	28	80	0.35	24
	10	38	115	0.33	59	T20,C4	34	90	0.38	40
	11	74	114	0.65	55	T50,C4	45	224	0.20	25
		39.0† ±23.8(8)	99.0 ±25.1(8)	0.37‡ ±0.21(8)	56.3 ± 8.1(11)		30.7§ ±13.0(10)	123.6 ±50.4(10)	0.26‡‖ ±0.11(10)	33.1¶ ±10.4(10)
Nondrug-induced Psychotics		67.4 ±32.7(18)	107.7 ±49.8(18)	0.66 ±0.34(18)	56.2 ±11.7(25)		59.6 ±23.0(23)	171.9¶ ±79.5(23)	0.43¶ ±0.25(23)	33.4¶ ± 9.5(20)
Inmate controls		57.1 ±15.3(15)	92.9 ±27.3(15)	0.64 ±0.15(15)	...		...	...	...	...

* Values for 5HIAA and HVA are nanograms (free acid) per milliliter CSF. Values for groups are mean ± SD (number of determinations). Drugs are trifluoperazine (T), chlorpromazine (CPZ), and benztropine (C).

† $P < .05$ vs 2 and 3. ‡ $P < .05$ vs 2, $< .002$ vs 3. § $P < .001$ vs 2. ‖ $P < .05$ vs 2. ¶ $P < .02$ compared to pretreatment value.

tient group; namely, psychotic without delerium and responsive to a single phenothiazine compound to the point of clinical remission.

At the time of the initial CSF sampling no patient had received psychoactive compounds for at least two weeks. The time which had elapsed since the drug ingestion leading to hospitalization was seven to 14 days. A second CSF sample using probenecid was obtained following remission of the psychotic state while the patient was taking phenothiazines. The interval between the two CSF samples varied from two weeks to three months; the clinical criteria for timing of the second spinal tap was remission of the psychotic state at a stable phenothiazine dose.

Mean values for lumbar CSF 5HIAA, HVA, and 5HIAA/HVA in the drug-induced group prior to phenothiazine treatment were compared to these values in the entire nondrug-induced psychotic group, and in a group of paid inmate volunteers (men, mean age 32). (The nondrug-induced psychotic group was not further subdivided, as it was in the clinical paper, since we intend to report our neurochemical findings for this group in detail at another time). The same metabolite measures were compared during phenothiazine treatment for the drug and nondrug psychotic groups. Intragroup comparisons between the pretreatment and treatment conditions were made using metabolite values and total Brief Psychiatric Rating Scale (BPRS) scores for both psychotic groups. We used a two-tailed *t*-test in each instance (unpaired).

Results

The Table shows the results obtained when we compared the probenecid-induced values for lumbar CSF 5HIAA and HVA in the two groups. Prior to treatment the drug group demonstrated lower values for 5HIAA and for the ratio 5HIAA/HVA compared to the nondrug group and the controls. Since the HVA values were not different in the groups, a decrease in CSF 5HIAA formation seems likely in the drug group. During treatment, compared to nondrug patients, the drug group continues to show a significant decrease in CSF 5HIAA and the ratio 5HIAA/HVA. The difference in the HVA values between the groups during treatment was not quite significant ($P = .1$). Compared to the pretreatment condition, treatment values for HVA and 5HIAA/HVA were significantly different in the nondrug group only. Total BPRS scores declined significantly with phenothiazine treatment in both groups.

Comment

Prior to and during treatment with phenothiazines we found evidence of a significant mean decrease in lumbar CSF 5HIAA formation in the drug-induced psychotic group compared both to the nondrug-induced psychotic group and to inmate controls. The interpretation and significance of probenecid-induced values for lumbar CSF 5HIAA and HVA in clinical studies must be made with caution.[1,2] The problem of an incomplete blockade of the brain-CSF transport system for 5HIAA and HVA by probenecid makes intersubject comparisons difficult.[3] Age variations between groups may be significant if there are marked age differences between groups.[1,4] The age differences in the present groups are not great enough, however, to account for the differences found. We cannot be certain about the location of the neuronal source of the reported changes nor can we specify what metabolic or neuronal process may have been responsible for them. Recent evidence suggests that lumbar CSF 5HIAA may originate from metabolism of 5-hydroxytryptamine (5HT) both in spinal cord and brain.[5,6] Dietary tryptophan may affect brain 5HT metabolism in man, as it does in animals.[7] Although no dietary precautions were observed, drug and nondrug patients were admitted in essentially random sequence to the hospital and all received the regular hospital diet. All spinal taps were performed between 1 and 2 PM. There is a large literature dealing with the effects of adrenal hormones and stress procedures upon 5HT metabolism in animals.[8] In general, acute administration of certain adrenal steroids and short periods of stress may

decrease brain 5HT turnover in rats, possibly by producing a transient increase in tryptophan pyrrolase activity of the liver. Periods of immobilization stress for rats greater than four hours apparently produce an increase in brain 5HT turnover. The more chronic stress model seems most analagous to our patients, although the change we found is in the direction opposite to that which the model would predict. Further, the fact that our findings of decreased 5HIAA formation persisted into the period of remission suggests that the results were not related simply to a stress variable.

It is interesting to note that the effects we have described here for the drug group are similar to the findings in animals following acute doses of psychotomimetic drugs, noteably LSD. Acute doses of LSD in animals increase brain 5HT[9] and decrease brain 5HIAA,[10] probably as a consequence of the selective inhibitory effect this compound has upon indole-containing neurons in the midbrain raphe.[11] Other 5HT-containing neurons in the central nervous system might be similarly affected. However our subjects had not ingested a psychotomimetic drug for at least several days prior to the first CSF sample. One might postulate that in man the psychotic reaction induced by LSD-like drugs can be associated with the persistence of an acute pharmacological effect of these drugs; namely, a decrease in the activity of 5HT-containing neurons manifest by a decrease in CSF 5HIAA formation. Another possibility is that the 5HIAA findings were present prior to the use of LSD-like drugs and in some way rendered the individual patient more susceptible to the disruptive effects of these compounds. In this regard, we have previously reported a subgroup of depressives who became psychotic during treatment with amitriptyline alone and noted that most of these individuals showed decreased CSF 5HIAA formation prior to treatment.[12] Amitriptyline hydrochloride appeared to produce an additional decrease in 5HIAA formation in most of these depressive patients, including those who did not become psychotic. Amitriptyline hydrochloride and other tertiary amine tricyclic antidepressants block a reserpine-resistant 5HT uptake mechanism and thus presumably facilitate the action of 5HT at the receptor.[13-15] The acute LSD effect has been explained as a negative feedback upon 5HT-containing neurons as a result of an interaction between LSD and 5HT receptors.[11,16,17] Relating such hypotheses to the present report, we might suggest that in some instances the use of LSD-like drugs may result in an irreversible (or slowly reversible) effect upon 5HT receptors, giving rise to a state of persistent receptor stimulation and a negative feedback upon 5HT synthesis. A direct effect upon 5HT neurons is also conceivable. Whatever the ultimate explanation, our data show that in some patients with drug-induced psychotic reactions, the CSF acid monoamine metabolite findings are consistent with the acute LSD findings in animals showing that 5HT turnover in the central nervous system is decreased. It should be noted that long-term administration of LSD to rats has been reported to increase, rather than decrease, brain 5HT turnover.[18]

During treatment, we found significant increases in CSF HVA and decreases in the 5HIAA/HVA ratio in the nondrug group only. Thus there is some suggestion that the drug group was less responsive than the nondrug group to phenothiazines (despite a similar mean maintenance phenothiazine dose) in terms of an increase in CSF HVA. However, even in the drug group, the larger phenothiazine doses appear to be associated with increases in CSF HVA formation. The effect of phenothiazines to increase HVA formation in animal brain is well known,[19] and an increase in basal levels of HVA following phenothiazines has been reported in human lumbar CSF.[20,21]

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Nonproprietary and Trade Names of Drug

Amitriptyline hydrochloride–*Elavil Hydrochloride.*

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