

# Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium

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## Abstract

This study sought to investigate possible interactions between antidepressant agents and lysergic acid diethylamide (LSD) in humans through the use of retrospective questionnaires. Ten subjects were identified who used LSD during chronic (3 weeks or longer) periods of antidepressant administration. These subjects were asked to describe the phenomenological effects of self-administered hallucinogens prior to and during antidepressant treatment; a structured, standardized questionnaire was used to evaluate LSD experiences. Chronic tricyclic antidepressant administration was associated with subjective increases in physical, hallucinatory and psychological responses to LSD. Similarly, subjects receiving lithium chronically also reported increases in their responses to LSD. In contrast, subjects who had been chronically taking an monoamine oxidase (MAO) inhibitor reported subjective decreases in the effects of LSD. This is similar to a previous report by our group of a decreased response to LSD in individuals who were chronically taking serotonin-selective antidepressants. These altered responses to LSD most likely involve differential changes in central serotonin and dopamine receptor systems and are consistent with other recent data suggesting that the clinical efficacy of different classes of antidepressants may not necessarily rely on a common mechanism of action in the brain.

*Keywords:* Lithium; Lysergic acid diethylamide; Monoamine oxidase; Tricyclic antidepressant; Chronic drug administration

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## 1. Introduction

The self-administration of recreational drugs by individuals who are being treated with antidepressants has long been recognized by the medical community. The present study describes responses to the hallucinogen, lysergic acid diethylamide (LSD), in individuals being treated with tricyclic antidepressants, lithium or monoamine oxidase (MAO)-inhibiting antidepressants on a long-term basis.

Chronic administration of tricyclics, lithium or MAO inhibitors has been frequently shown to induce a down-regulation of both  $\beta$ -adrenergic receptors and 5-hydroxytryptamine (5-HT)<sub>2</sub> receptors in the brain [16,23]. As the characteristic effects of hallucinogenic drugs are thought to specifically involve activation of 5-HT<sub>2</sub> receptors [13], the human response to LSD might be noticeably altered following treatment with antide-

pressant drugs. Previous studies have suggested that chronic administration of MAO inhibitors decreased the effects of LSD in human subjects [15,28]. Two recent reports described reduced responses to LSD in individuals taking serotonin-selective antidepressants, including fluoxetine and sertraline [4,36].

## 2. Methods

Methods for this study have been described elsewhere [4]. In brief, subjects were recruited through advertisements placed on selected computer Internet newsgroups requesting an interview with hallucinogen users who had ingested LSD or similar drugs during the time that they had been taking a physician-prescribed antidepressant. A structured interview was conducted orally or in written form using a standardized questionnaire which consisted of queries about the antidepressant treatment (drug, daily dose, length of time on antidepressant when the hallucinogen was ingested, reason for being placed on the antidepressant); about other medical or recrea-

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tional drugs that the subject used on a regular basis; and about the phenomenological effects of the hallucinogen that had been taken during antidepressant treatment. In order for a report from a subject to be considered usable, the subject must have had a 'control' condition with which to compare the current hallucinogen experience. All subjects in this study had extensive prior experience with a range of LSD doses prior to antidepressant use. In addition, 6 of 10 subjects had experimented with the same batch of LSD both before and during antidepressant treatment. All subjects also had friends who had taken the same dose of LSD from the same batch as the subject but were not taking an antidepressant, thus providing reference experiences with which the subject could compare her or his response to LSD. Subjects who wished to participate in this study were assured of confidentiality prior to being interviewed. A complete copy of the structured interview is available upon request.

### 3. Results

Summations of the case reports compiled from individual interviews are presented in Table 1.

Information in the table follows the outline of the questions in the structured interview. In addition to the reports of our subjects' responses to LSD during chronic administration of an antidepressant, certain subjects were able to provide data on their response to the hallucinogen during or after withdrawal from an antidepressant.

All of the five subjects interviewed who had been chronically taking a tricyclic antidepressant (imipramine, desipramine or clomipramine) reported an overall subjective increase in their physical, hallucinatory and psychological response to LSD. Subjects noted an increase in 'somatic distortion' from the hallucinogen compared to times prior to antidepressant use, as well as 'more psychic energy' throughout the experience. Hallucinations were described as 'more elaborated', 'livelier' and 'perkier' than would have been expected based on the dose of LSD ingested, with one subject reporting that he saw 'a continuous sunrise for over an hour' while sitting outside at night. Even with a reduction in desipramine dose during withdrawal, one subject reported his response to LSD was still potentiated. However, following several months of complete withdrawal from either desipramine or clomipramine, two subjects stated

Table 1

	Age	Sex	Diagnosis	Antidepressant dose (mg/day)	Weeks	LSD dose	Onset of effects	Physical effects	Halluc. effects	Psych. effects	Total time	Sleep	Overall response
<b>Imipramine</b>													
A	26	M	depression	200	8	80 µg	↓	↑	↑	↑	↓	↑	↑
B	28	M	depression	175	40	200 µg	↓	↑	↑	↑	↑	n.c.	↑
<b>Desipramine</b>													
C	27	M	depression	200	150+	150 µg (40 ×)	↓	↑	↑	↑	↑	↓	↑
				100	3–24	150 µg (20 ×)	↓	↑	↑	↑	↑	↓	↑
				(withdrawal)	12	150 µg	n.c.	↑	↑	↑	↑	n.c.	↑
				(withdrawal)	20	150 µg	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
D	32	M	depression	200	100	100 µg	↓	↑	↑	↑	↑	↓	↑
<b>Clomipramine</b>													
E	25	M	alcoholism	125	12	('moderate')	↑	↑	↑	↑	n.c.	n.c.	↑
				(withdrawal)	12	('moderate')	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
<b>Lithium</b>													
F	27	M	depression	600	32	('moderate')	↓	↑	↓	↑	↑	↓	↑
G	21	M	normal vol.	1000	7	('high-moderate')	↓	n.c.	↑	↑	↓	n.c.	↑
<b>(+ 175 mg/day imipramine for 4 weeks)</b>													
H	29	M	depression	1000	50	200 µg	↓	↑	↑	↑	↑	↓	↑
<b>MAO INHIBITORS</b>													
<b>Phenelzine</b>													
I	22	M	depression	75	12	150 µg	n.c.	↓	↓	↓	↓	n.c.	↓
<b>Phenelzine (+ 30 mg/day tranylcypromine)</b>													
J	25	M	depression	60	12	('moderate')	n.c.	↓	↓	↓	n.c.	n.c.	↓

Data in this table were drawn from structured interviews with 10 subjects concerning subjective assessments of their responses to LSD during chronic administration of an antidepressant, as described in the text. All doses of LSD are estimates provided by subjects based on prior experience with hallucinogens. Halluc. effects = hallucinatory effects; Psych. effects = psychological effects; ↑ symbol indicates an increase in response; ↓ symbol indicates a decrease in response; n.c., indicates no change in response. An arrow indicating 'increase' in onset of effects means it took longer than normal for the effects of LSD to first be felt, while a 'decrease' in onset of effects means the effects were first felt sooner than normal. When the response occurred following complete withdrawal from the antidepressant, 'withdrawal' is noted, with the number of weeks of withdrawal listed at time of LSD ingestion.

that their responses to LSD were no longer increased compared to normal.

Similar to the effects of the tricyclic antidepressants, subjects who had been chronically taking either lithium alone or in combination with imipramine stated they had increased responses to LSD. All of three subjects interviewed observed hallucinations that had 'more visual sharpness' or were much greater in intensity than the 'normal reality with hallucinogenic overlay' which had been expected. One subject also experienced auditory hallucinations that were self-critical, accompanied by the inability to form words, both of which had never happened to him before. Another subject described 'unrelenting' physical and psychological stimulation which made for a 'tedious and trying' experience.

In contrast to responses with tricyclic antidepressants or lithium, both of the two subjects interviewed who had been chronically taking an MAO inhibitor (phenelzine or phenelzine plus tranylcypromine) had a near abolishment in their subjective responses to LSD. Both subjects had few noticeable physical or psychological effects occur following hallucinogen ingestion. One subject noted only 'perhaps a slight intensification of colors' compared to his usual visual field while the other subject did not discern any hallucinogenic response at all.

#### 4. Discussion

The data presented in this paper indicate that the human response to LSD can be substantially altered by long-term administration of antidepressants. Those subjects in the present study who were chronically taking either tricyclic antidepressants or lithium reported a potentiation in the subjective effects of LSD, while those subjects who had chronically been taking an MAO inhibitor reported a decrease in their subjective responses to the hallucinogen. Previous investigations indicate that chronic administration of MAO inhibitors [15,28] or serotonin-selective antidepressants [4,36] can reduce the human hallucinogenic response. While there are limitations and possible biases in this type of retrospective study, some of these concerns may have been mitigated by: (1) the use of a standardized questionnaire; (2) all subjects had extensive experience with LSD prior to antidepressant use; (3) subjects reported both increased and decreased responses to LSD, dependent on the class of antidepressant they were taking. The sample size in this study is limited because of the difficulty in recruiting potential subjects to discuss illegal drug use with researchers who work at a government facility. In addition, fewer people are being prescribed tricyclic antidepressants, lithium or MAO inhibitors for depression with the advent of serotonin-selective reuptake inhibitors. However, the fact that there is consistency of response to LSD for people who were taking

the same class of antidepressant suggests that these case reports may be representative of the subjective responses which occur when antidepressants are combined with LSD.

There is much evidence supporting a down-regulation in  $\beta$ -adrenergic receptors and 5-HT<sub>2</sub> receptors as well as other adaptational consequences that follow chronic administration of many antidepressant drugs [16,23]. Since biochemical and behavioral studies have suggested that the primary central action of LSD may rely upon stimulation of 5-HT<sub>2</sub> receptors [14,29,38,41], it might have been anticipated that the chronic administration of the antidepressants in this study would have reduced the human response to LSD. Chronic administration of imipramine also reduces [<sup>125</sup>I]LSD binding in rat cortex [8]. However, since the present data show that only MAO inhibitors decreased the effects of LSD, other pharmacological mechanisms must also play a role in the way an antidepressant can affect the subjective response to a hallucinogen.

Chronic administration of the tricyclic antidepressant desipramine has been demonstrated to enhance the inhibitory effects of iontophoretically applied LSD or 5-HT on forebrain neurons, an effect which was interpreted as a sensitization of postsynaptic serotonin receptors [10]. This response was not seen following chronic administration of the serotonin-reuptake inhibitor, fluoxetine. Similar increases in the sensitivity of hippocampal neurons following chronic administration of imipramine or clomipramine to applied 5-HT [11] or of amygdaloid neurons to LSD or 5-HT after chronic desipramine or imipramine [39] have also been noted. In contrast, chronic administration of tricyclic antidepressants does not alter presynaptic 5-HT<sub>1A</sub> receptor-mediated responses to LSD in the dorsal raphe nucleus [3,37]. Thus, electrophysiological studies in rat forebrain areas provide data regarding serotonergic changes in keeping with our observations in humans.

Additionally, dopamine systems may contribute to the potentiated response to LSD reported with tricyclic antidepressants. LSD has long been known to have dopamine agonist effects in the brain [25], and [<sup>3</sup>H]LSD has been shown to bind at post-synaptic dopamine receptors [6,7]. Chronic administration of desipramine has been shown to enhance the behavioral response to the dopamine agonist, amphetamine, an effect which was not seen following chronic administration of fluoxetine [35]. Similarly, the behavioral effects resulting from the dopamine agonist quinpirole [20] or high doses of apomorphine [32] were also increased after chronic imipramine or clomipramine treatment. These effects may be occurring through a change in dopamine receptor sensitivity, since chronic administration of imipramine has been demonstrated to enhance agonist affinity for D2 receptors [19]. Although clomipramine is often

categorized as a serotonergic antidepressant, it is also a potent dopamine reuptake inhibitor [27].

The potentiation of the human response to LSD in the present study following chronic administration of lithium may depend on complex mechanisms. 5-HT<sub>2</sub> binding in rat brain was reduced after chronic lithium treatment [24], as were the inhibitory effects of LSD on 5-HT release [40]. These latter changes are suggestive of a desensitization of serotonin autoreceptors. In addition, chronic lithium blocked the facilitatory effect of LSD on shock-elicited fighting in rats [21] but did not alter [<sup>3</sup>H]LSD binding in a variety of brain regions [17]. However, although acute and subchronic administration of lithium may increase serotonin levels in the brain, chronic administration of lithium has been shown to decrease 5-HT concentrations [26,33]. This may be important since it has been suggested that LSD is a partial agonist, with its effects dependent on endogenous 5-HT concentrations [31]. Since levels of 5-HT are reduced after chronic lithium, this may allow LSD to act as an agonist behaviorally and thus account for the data in the present investigation. Previous work with drugs that deplete serotonin have demonstrated that *para*-chlorophenylalanine [1] or 5,7-hydroxytryptamine [2] enhance the behavioral response of rats to LSD.

Earlier clinical studies have demonstrated that chronic administration of the MAO inhibitors nialamide [15] or isocarboxazide [28] abolished the LSD response in human subjects. Animal studies have similarly shown that chronic phenelzine administration can decrease the LSD discriminative cue in rats [9] as well as reduce the disruption of FR-40 responses induced by LSD [34]. Since MAO inhibitors can reduce 5-HT<sub>2</sub> receptors when given chronically [23], these reduced behavioral responses may reflect the fact that there are fewer sites where LSD can act as a partial 5-HT<sub>2</sub> agonist. In addition, chronic administration of clorgyline [22] or phenelzine [18] has also been shown to increase brain 5-HT concentrations, suggesting the conditions necessary for the partial agonist LSD to act as an antagonist. This, then, also might contribute to the decrease in response to LSD in the present study following chronic phenelzine administration.

It is interesting to note parallels between the effects of chronic antidepressant treatment on LSD response in the current study and on psychotic symptoms in schizophrenic patients. When individuals exhibiting positive symptoms of schizophrenia were given imipramine chronically, without neuroleptic medication, there was an exacerbation of hallucinations [12], similar to the potentiated response to LSD seen in our subjects who had chronically been taking imipramine. Conversely, a review of chronic treatment with MAO inhibitors in schizophrenic patients indicated that 47% had a reduction in hallucinations [5], similar to the reports of

decreased response to LSD in our subjects who had been taking phenelzine chronically.

In summary, the chronic administration of medically-prescribed antidepressants to humans appears to have a substantial effect on subjective responses to self-administered hallucinogenic drugs. Whether these responses are increased or decreased is dependent on which class of antidepressant drugs had been taken and may involve changes in both serotonin and dopamine systems. Recent clinical investigations support this interpretation in demonstrating that there need not be a single mechanism of action which must account for the clinical efficacy of antidepressants. A review Salomon et al. by [30] cites studies in which the therapeutic effects of serotonin-selective reuptake inhibitors can be reversed by tryptophan depletion, but not by depletion of catecholamines following  $\alpha$ -methyl-*para*-tyrosine (AMPT) administration, whereas the efficacy of the tricyclic antidepressant, desipramine, was reversed by AMPT but not by tryptophan depletion. Additional investigations of the possible mechanisms underlying these differential alterations in response to LSD are currently being pursued in our laboratory using behavioral and biochemical experiments in animal models.

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