Is Depersonalization Disorder Initiated by Illicit Drug Use Any Different? A Survey of 394 Adults

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Objective: Previous studies have documented that in a substantial minority of individuals with depersonalization disorder, onset is first triggered by illicit drug ingestion. The goal of this study was to systematically compare a large sample of individuals with drug-initiated (D) versus non–drug-initiated (ND) chronic depersonalization.

Method: We conducted an internet survey of 394 adults endorsing *DSM-IV-TR* depersonalization and/or derealization symptoms. Sixty-four questions were utilized to inquire about demographic and clinical characteristics, illness course, substance use history, and treatment response. The Cambridge Depersonalization Scale (CDS) was administered. The study was conducted from September 2005 to January 2006.

Results: Compared to the ND group (n = 198), the D group (n = 196) included more male and younger individuals. The 2 most common precipitating drugs were cannabis and hallucinogens, followed by ecstasy. The majority of participants had modest use histories prior to onset and never ingested subsequently. The 2 groups endorsed similar illness course, impairment, suicidality, and limited treatment response. The D group showed significantly greater improvement over time than the ND group ($P = .002$), although the groups did not differ in reported psychotherapy or pharmacotherapy effectiveness. The groups did not differ in CDS total score or on the 4 subscale scores of unreality of self, perceptual alterations, unreality of surroundings, and temporal disintegration. On the numbing subscale of the CDS, the ND group scored higher ($P = .009$) only prior to controlling for age and gender.

Conclusion: The study strongly supports a uniform syndrome for chronic depersonalization/derealization regardless of precipitant.

J Clin Psychiatry 2009;70(10):1358–1364

Submitted: *May 12, 2008; accepted October 8, 2008.*
Online ahead of print: *June 16, 2009 (doi:10.4088/JCP.08m04370).*
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Depersonalization disorder (DPD) is a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[1] dissociative disorder characterized by persistent or recurrent depersonalization symptoms in the presence of intact reality testing, not better accounted for by other psychiatric or medical disorders. Its prevalence in the general population has been estimated at 1% to 2%,[2] yet it remains poorly researched, underdiagnosed, and without established treatment guidelines. Recently, 2 large, systematic, independent cohorts of well-characterized DPD patients have definitively established the presentation and clinical characteristics of the disorder, describing impressively consistent nosology.[3,4] Furthermore, development of the well-validated Cambridge Depersonalization Scale (CDS)[5] now permits a more accurate quantification of depersonalization and derealization experiences and has led to the delineation of several distinct symptom dimensions in those affected.[6,7]

Interestingly, in both cohorts,[3,4] a substantial minority of cases were drug-triggered in onset, an observation anecdotally reported 2 decades earlier.[8,9] In a US cohort of 117 cases,[3] 22% identified drug precipitants for the disorder, specifically cannabis (13%), hallucinogens (6%), ecstasy (2%), and ketamine (1%). Similarly, in a UK cohort of 164 individuals,[10] 24% identified drugs as precipitants for the disorder: 12% for cannabis, 2.4% for ecstasy, 1.2% for lysergic acid diethylamide (LSD), and 0.6% for ketamine. In the latter study, comparison to the non–drug-triggered group revealed that the drug-triggered group was significantly younger and had a preponderance of male subjects. Otherwise, the 2 groups were reported to be "strikingly" similar in phenomenology and clinical characteristics, especially when 2 subgroups were subsequently compared that were age and sex matched. Based on this sample, the authors concluded that "drug-induced" DPD probably does not represent a "distinct clinical syndrome."[10(p1731)]

The issue of drug-triggered DPD is an important one, for 2 reasons. One, dissociative disorders are broadly conceptualized as stress or trauma related, with substantial literature supporting this conceptualization.[11] In this framework, DPD has remained somewhat of a puzzle, as a substantial portion (27%–49%) of patients do not, of their own accord or by clinician assessment, present with stress-related precipitants

or histories, while a comparable portion does report such histories.[3,4] This stands in some contrast to other dissociative disorders such as dissociative amnesia, dissociative fugue, and dissociative identity disorder, in which traumatic or stressful antecedents are almost ubiquitous, leading some experts to question whether DPD really belongs with the dissociative disorders or might be better classified with anxiety or mood disorders.[4] However, neurobiologic studies in DPD have so far revealed patterns differing from anxiety and mood disorders and compatible with studies in other dissociative conditions.[12–18] Second, if indeed drug- and non–drug-triggered DPD have few differences, such a finding begs for a unified conceptual model for the disorder and its underlying neurobiologic substrates, regardless of antecedents.

Thus, the goal of this study was to systematically explore in a large sample whether there is any descriptive evidence for heterogeneity in the chronic depersonalization syndrome, ie, whether the drug- and non–drug-induced syndromes are distinct. To this end, drug- and non–drug-triggered participants were surveyed, allowing detailed comparisons of demographic and clinical characteristics, symptomatology, time course, and treatment response.

METHOD

Participants were 394 individuals who completed an Internet survey entitled, "Depersonalization/Derealization Study," approved by the Mount Sinai School of Medicine institutional review board with a waiver of informed consent. The study was conducted from September 2005 to January 2006. Data were gathered in an anonymous fashion, whereby individuals applied for a password and subsequently completed the survey on the one Web site in which it was posted (National Organization for Drug-Induced Disorders, www.nodid.org). Participants were self-referred to the Web site, referred by other depersonalization informational Web sites, or referred by our institution's depersonalization research program. The survey first presented the *DSM-IV-TR* verbatim definitions of depersonalization and derealization, respectively, as "an alteration in the perception or experience of the self so that one feels detached from, and as if one is an outside observer of, one's mental processes or body (eg, feeling like one is in a dream)" [1(p.)] and as "an alteration in the perception or experience of the external world so that it seems strange or unreal (eg, people may seem unfamiliar or mechanical)."[1(p766)] The survey then inquired of participants: "Do you have depersonalization/derealization?" Only individuals who responded "yes" to this question were instructed to proceed with the survey.

The survey included 65 questions in total, aimed at investigating the demographic and clinical characteristics, illness course, and treatment history of individuals whose chronic depersonalization/derealization (CDD) was initially precipitated by drug ingestion versus not. For individuals who attributed the onset of CDD to drugs, several sets of questions were designed to elicit specific information regarding the precipitating ingestion, kind of drug "trip," onset of CDD with respect to the triggering ingestion, prior lifetime drug history, and drug use subsequent to the precipitating ingestion and its impact on CDD. Drugs were categorized as follows, in the same fashion for all related questions: alcohol, cannabis, hallucinogens, ecstasy, dissociatives (ketamine, aka "Special K"), stimulants (methamphetamine, amphetamine), downers (sedatives, hypnotics, anxiolytics), opioids, cocaine/crack, inhalants, and 2 additional options of "other drugs." To inquire about psychopharmacologic treatment history, medications were categorized as follows, with examples in each category: stimulants, traditional antipsychotics, atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs), opiates, opiate blockers, barbiturates, benzodiazepines, anticonvulsants, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) , β blockers, lithium, and 2 additional options for other medications.

All questions inquiring about change in symptoms, whether during the natural course of the CDD or treatment related, employed the standard 7-point Clinical Global Impressions-Improvement scale (CGI-I),[19] ranging from 7 (very much worse), to 4 (no change), to 1 (very much improved). Participants also completed the CDS,[5] a comprehensive 29-item self-report scale inquiring about subjective experiences classically associated with the depersonalization syndrome. Each item is rated on 2 Likert scales quantifying frequency (range, 0–4) and duration (range, 1–6), yielding a total score ranging from 0 to 10; CDS total score is the arithmetic sum of all items (range, 0–290). The scale has high internal consistency (Cronbach's $\alpha = 0.89$) and has been found to effectively differentiate DPD from healthy controls, temporal lobe epilepsy, and anxiety disorders; a cutoff score of 70 yields 75.5% sensitivity and 87.2% specificity for the disorder.[5] In addition to CDS total score, subscale scores for the 5 symptom domains of numbing, unreality of self, perceptual alterations, unreality of surroundings, and temporal disintegration were calculated, factor-analytically derived from this study sample.[7] The Sheehan Disability Scale[20] was also administered, asking participants to rate their disability in 3 life domains (work/school, social life, family life/home) as a result of having CDD, on a scale from 1 to 10. All questions were numerically coded, with forced responses from a drop-down menu in order to be able to proceed to the next question, thus not allowing missing responses. If only a single item was to be chosen as an answer to a particular question, then the survey was programmed to allow only a single answer.

Comparisons between the 2 groups employed independent sample t tests or χ^2 tests as appropriate, as well as analysis of covariance to control for age and gender effects. Given the multiple comparisons for CDS subscale and individual item scores, a significance level of .01 was preselected (2 tailed). All other comparisons employed a 2-tailed level of significance of .05.

Table 1. Frequency Distribution of Chronic Depersonalization/Derealization Duration in 394 Surveyed Adults

Duration	No. of Individuals	% of Total Sample
< 1 mo	13	3.3
1–3 mo	15	3.8
4–6 mo	25	6.3
7–12 mo	29	7.4
>1 to 3 y	77	19.5
4–6 y	70	17.8
7–10 y	43	10.9
11–20 y	58	14.7
21–30 y	36	9.1
> 30 y	28	7.1

RESULTS

Total Sample Characteristics

The survey was completed by 394 adults, 159 women and 235 men, aged 18 to 88 years (mean age = 28.8, SD = 10.2). Participants' race was 90.4% white, 3.3% Hispanic, 1.5% Asian, 0.3% African American, 0.3% Native American, and 4.3% other. Marital status was 64.0% single, 17.8% married, 10.9% common-law partners, 5.1% divorced, 2.0% separated, and 0.3% widowed. Highest education attained was as follows: 10.7% did not finish high school, 15.2% were high school graduates, 39.1% had some college, 24.6% were college graduates, and 10.4% had some advanced education. Employment status was 25.6% unemployed, 35.5% full-time employed, 8.1% part-time employed, 18.0% full-time student, 2.5% part-time student, 3.6% homemaker, and 6.6% part-time work and school.

Of the total sample, 92.1% had current CDD at the time of the survey. Of the 31 individuals who did not endorse current CDD, 11 had been in remission for 1 year or less, 11 for 2 to 5 years, and 9 for more than 5 years. Mean age at onset of CDD was 18.0 years (SD = 6.8; range, 3–48), with a mean duration of 10.9 years (SD = 11.1). Table 1 presents the illness duration frequency distribution. About two thirds of the sample (69.3%) endorsed a continuous course of illness, while about one third (30.7%) endorsed it as episodic. Functional impairment due to the CDD was rated as 6.9 (SD = 2.7) for work/school, 7.3 (SD = 2.5) for social life, and 6.3 (SD = 2.7) for home and family life. Fifty-five individuals (14.0%) were on disability because of their CDD. A substantial minority (17.0%) endorsed psychiatric hospitalization for CDD. The majority of participants (67.0%) had considered suicide attributed to CDD, and 10.9% had attempted suicide attributed to CDD.

Mean CDS total score was 120.0 ± 54.4, and 80% of participants had a CDS score above the recommended cutoff of 70 for the diagnosis of depersonalization disorder. Cambridge Depersonalization Scale total score was not significantly associated with age at onset ($r = -0.02$, $P = .71$) or illness duration ($r = 0.05$, $P = .34$) but was significantly associated with functional impairment in all 3 life domains (r range, 0.37–0.42; $P < .001$). One third of the sample (33.2%) endorsed having been diagnosed with "depersonalization disorder" by a professional. Of those diagnosed with the disorder, the following numbers of professionals were seen until the disorder was accurately diagnosed: 1 (21.2%), 2 (20.5%), 3 (17.4%), 4 (12.9%), and 5 or more (28.0%). Compared to when the CDD started, participants rated their current condition as follows: 8 (2.2%) very much better, 46 (12.7%) much better, 116 (32.0%) minimally better, 65 (17.9%) unchanged, 53 (14.6%) minimally worse, 48 (13.2%) much worse, and 27 (7.4%) very much worse.

More than half of participants (57.1%) had received "psychotherapy (talk therapy) of any kind" for CDD and rated its outcome for CDD as follows: 1.3% very much improved, 8.4% much improved, 26.4% minimally improved, 57.8% no change, 0.3% minimally worse, and 0.3% much worse. Of the total sample, 250 (63.5%) endorsed having received medication treatment of CDD. The following medication trials were reported in order of decreasing frequency: SSRIs, N = 200 (mean CGI-I score = 3.8); benzodiazepines, N = 124 (CGI-I = 3.2); atypical antipsychotics, N = 73 (CGI-I = 4.6); tricyclics, N = 48 (CGI-I = 4.4); anticonvulsants, N = 41 (CGI-I = 3.8); typical antipsychotics, N = 31 (CGI-I = 4.5); stimulants, N = 28 (CGI-I = 4.1); β blockers, N = 26 (CGI-I = 4.0); MAOIs, N = 16 (CGI-I = 3.7); lithium, N = 10 (CGI-I = 4.1); serotonin-norepinephrine reuptake inhibitors, N = 5 (CGI-I = 3.6); opiates, N = 5 (CGI-I = 4.4); mirtazapine, N = 4 (CGI-I = 3.5); opioid antagonists, N = 4 (CGI-I = 5.0); barbiturates, N = 4 (CGI-I = 4.5); and bupropion, N = 3 (CGI-I = 3.3). Medication trials endorsed by fewer than 3 individuals are not reported for brevity. It can be seen that no medications approached the efficacy traditionally considered a positive treatment response (CGI-I score of 2 or 1).

Characteristics of Drug-Initiated CDD

Of the whole sample, 196 endorsed chronic depersonalization first initiated by drug use, whereas 198 did not. Table 2 presents the substances that participants had ingested and attributed their CDD to when it first started. Although alcohol was frequently taken with the precipitating drug ingestion (27.6%), no participants attributed their CDD to alcohol. During the intoxication that led to the CDD, 87.2% of subjects endorsed having a "bad trip." For participants with CDD triggered by the 3 most common monoingestions, Table 3 presents pertinent information regarding prior lifetime use history for the particular drug, time course between ingestion and onset of CDD, and subsequent use history for the particular drug and its impact on the CDD.

Comparison of the Drug- (D) Versus Non–Drug- (ND) Initiated Groups

With respect to demographic characteristics, the 2 groups differed in age (mean ± SD, D: 27.7 ± 10.2 years; ND: 30.0 ± 10.2 years; $t = 2.22$, $P = .027$) and gender (D: 139 men

Table 2. Drug Ingestions to Which Initiation of Chronic Depersonalization/Derealization Was Attributed by 196 Survey Participants

Drug Types	n	%
Monoingestions		
Cannabinoids	89	45.4
Hallucinogens	26	13.3
Ecstasy	8	4.1
Dissociatives	1	0.5
Stimulants	0	0
Downers	0	0
Opioids	0	0
Cocaine	0	0
Inhalants	0	0
Other: salvia	1	0.5
Unknown	9	4.6
Polyingestions (overlapping)	61	31.1
Cannabinoids	55	28.1
Hallucinogens	40	20.4
Ecstasy	19	9.7
Dissociatives	8	4.1
Stimulants	12	6.1
Downers	8	4.1
Opioids	2	1.0
Cocaine	6	3.1
Inhalants	4	2.0
Other: salvia	3	1.5

Table 3. Drug Use History and Relationship to Chronic Depersonalization/Derealization (CDD) Onset for the 3 Most Common Monoingestions (n = 123)

Drug Use History	Cannabinoids (n = 89)	Hallucinogens (n = 26)	Ecstasy (n = 8)
Lifetime drug use prior to onset, n (%)			
Never	6 (6.7)	4 (15.4)	6 (75.0)
Once	6 (6.7)	2 (7.7)	0 (0.0)
2–10 times	20 (22.5)	11 (42.3)	1 (12.5)
11–50 times	24 (27.0)	7 (26.9)	1 (12.5)
51–100 times	8 (9.0)	0 (0.0)	0 (0.0)
100–500 times	25 (28.1)	2 (7.7)	0 (0.0)
> 500 times	0 (0.0)	0 (0.0)	0 (0.0)
Time of onset after ingestion, n (%)			
Immediate/during intoxication	59 (66.3)	6 (23.1)	1 (12.5)
Within 24 h	11 (12.4)	4 (15.4)	4 (50.0)
Within 72 h	3 (3.4)	4 (15.4)	0 (0.0)
Within 1 wk	5 (5.6)	4 (15.4)	2 (25.0)
Within 1 mo	11 (12.4)	8 (30.8)	1 (12.5)
Drug use subsequent to onset, n (%)			
Never used again	63 (70.8)	18 (69.2)	4 (50.0)
Tried again, effect of CDD			
No change	9 (10.1)	2 (7.7)	0 (0.0)
Minimally worse	6 (6.7)	3 (11.5)	1 (12.5)
Much worse	6 (6.7)	1 (3.8)	1 (12.5)
Very much worse	5 (5.6)	2 (7.7)	2 (25.0)

and 57 women; ND: 96 men and 102 women; $\chi^2 = 20.59$, $P < .001$), with a preponderance of younger and male participants in the drug-initiated group. The 2 groups did not significantly differ in race ($\chi^2 = 2.79$, $P = .732$), marital status ($\chi^2 = 10.34$, $P = .066$), education ($\chi^2 = 7.54$, $P = .274$), or employment ($\chi^2 = 2.55$, $P = .92$). Table 4 presents similarities and differences in the clinical characteristics of the 2 groups.

With respect to treatment history, more individuals in the non–drug-initiated group had received psychotherapy (D: 51.5%; ND: 62.6%; $\chi^2 = 4.95$, $P = .026$); however, the rated effectiveness (CGI-I) of psychotherapy did not differ between the 2 groups ($\chi^2 = 3.68$, $P = .597$). Similar proportions had received pharmacotherapy in the 2 groups (D: 64.3%; ND: 62.6%; $\chi^2 = 0.12$, $P = .732$), and the 2 groups did not differ in reported efficacy for any of the medication classes listed in Table 2 (statistics not presented for brevity).

We then examined CDS total, subscale, and item scores in the 2 groups. As noted above, the 2 groups differed in both age and gender. Cambridge Depersonalization Scale total score for the combined sample was not significantly associated with age ($r = 0.04$, $P = .435$), but correlations with age were in different directions within the 2 subgroups (D: $r = 0.12$, $P = .093$; ND: $r = -0.06$, $P = .415$). In addition, women had a significantly higher mean ± SD CDS total score in the combined sample (women: 135.0 ± 53.3; men: 109.9 ± 52.9; $t = 4.60$, $P < .001$) and in each group (D group, women: 131.5 ± 56.6; men: 108.8 ± 52.0; $t = 2.71$, $P = .007$) (ND group, women: 136.9 ± 51.5; men: 111.4 ± 54.5; $t = 3.38$, $P = .001$). Therefore, in comparing total and subscale scores between groups, we both examined raw scores and controlled for age and gender (Table 5). Finally, comparing all 29 individual item scores at the preselected .01 level of significance, only item 7 (flavor of meals no longer gives pleasure or distaste) differed between groups (D: 2.3 ± 3.2; ND: 3.3 ± 3.5; $t = 6.13$, $P = .002$) but the difference was no longer significant after controlling for age and gender.

CONCLUSION

This is the largest systematically studied group with chronic depersonalization, almost 400 individuals. Although self-report in nature and lacking diagnostics, the current sample had a mean ± SD CDS total score (120.0 ± 54.4) strikingly close to that of a large clinically diagnosed DPD sample (119.0 ± 58.9).[6] Furthermore, about 80% of survey participants reached the recommended threshold severity score for disorder diagnosis. The study revealed remarkable consistency in the nosology of the chronic depersonalization syndrome with the 2 earlier cohorts[3,4] with regard to symptomatology, age at onset, duration, course, morbidity, precipitating drug use, and treatment response. Consistent with other retrospectively collected treatment histories,[3] as well as the few published treatment trials,[21–23] the survey failed to report efficacy for any medication class. The slight and clinically marginal benefit from certain drug classes, in particular benzodiazepines, serotonin reuptake inhibitors, and stimulants, is consistent with prior reports,[3,21] as is the absence of any benefit from antipsychotics including atypicals.[3] Similarly, even though more than half the sample endorsed some kind of psychotherapy treatment, this was

Table 4. Comparison of Clinical Characteristics in the Drug- and Non–Drug-Initiated Groups

Clinical Characteristic	Drug-Initiated Group (n = 196)	Non–Drug-Initiated Group (n = 198)	Comparison χ^2/t	Comparison P
Age at onset of CDD, mean ± SD, y	18.8 ± 4.7	17.2 ± 8.3	2.43	.016
Duration of CDD, mean ± SD, y	8.9 ± 10.4	12.8 ± 11.4	3.56	< .001
Course, n			0.07	.794
Continuous	137	136		
Episodic	59	62		
Impairment, mean ± SD				
Work/school	6.9 ± 2.7	6.9 ± 2.7	0.01	.996
Social	7.5 ± 2.3	7.2 ± 2.6	1.23	.220
Family/home	6.3 ± 2.7	6.3 ± 2.6	0.05	.964
Disability, n	28	27	0.04	.852
Psychiatric hospitalizations, n	36	31	0.48	.488
Suicide attempts, n	21	22	0.01	.914
Current clinical status compared to onset, n			22.88	.002
Resolved	6	7		
Very much better	18	8		
Much better	27	19		
Minimally better	58	58		
Unchanged	36	29		
Minimally worse	30	23		
Much worse	11	37		
Very much worse	10	17		

Abbreviation: CDD = chronic depersonalization/derealization.

Table 5. Comparison of Cambridge Depersonalization Scale (CDS) Total and Subscale Scores Between the Drug- and Non–Drug-Initiated Groups

CDS	Drug-Initiated Group (n = 196)	Non–Drug-Initiated Group (n = 198)	Comparison[a] χ^2/t	Comparison[a] P	Comparison[a] P_c
Total score, mean ± SD	124.5 ± 54.4	115.4 ± 54.2	1.67	.097	.554
Subscale scores, mean ± SD					
Numbing	17.8 ± 14.2	21.9 ± 16.1	2.64	.009[b]	.065
Unreality of self	27.9 ± 15.3	30.8 ± 14.3	1.89	.059	.334
Perceptual alterations	12.0 ± 10.0	12.1 ± 9.9	0.11	.912	.363
Unreality of surroundings	12.5 ± 5.6	12.2 ± 6.3	0.46	.643	.473
Temporal disintegration	17.0 ± 9.8	18.0 ± 10.5	0.91	.362	.992

[a] P_c covaried for age and gender.
[b] Significance set at .01 level for subscale scores.

largely unsuccessful specifically in alleviating depersonalization symptoms.[3] Still, even though not inquiring about the specifics of therapy, it is very unlikely that participants received specialized therapies such as cognitive-behavioral therapy targeting DPD[24,25] or treatment targeting affect avoidance and alexithymia.[26]

Unlike previous studies, which mostly did not report on symptom severity as a function of gender, in this survey women rated their symptoms as significantly worse than men. A somewhat higher Dissociative Experiences Scale (DES)[27] score in female subjects compared to male subjects was reported in a prior sample,[3] but this difference was not statistically significant. However, the DES is less comprehensive in measuring depersonalization[28] compared to the CDS, which only measures depersonalization. Higher scores in female subjects in this sample could conceivably be related to greater traumatic stress histories in women or to more prominent mood and anxiety symptoms that could be exacerbating depersonalization severity.

The illicit drugs that were shown to induce chronic depersonalization in this large sample were similar to the previously reported ones,[3,4,10] primarily cannabinoids, hallucinogens, and ecstasy, whether as sole agents or in combination. Ketamine and salvia were less frequently endorsed culprits but are also less commonly ingested. Interestingly, opioids, cocaine, and stimulants have never been reported as triggers. Because the vast majority (87%) of study participants endorsed a bad trip on the occasion when the dissociation started, the data strongly suggest that the subjective quality of the intoxication experience may also contribute to triggering dissociation, especially if the "bad trip" was perceived as terrifying or life threatening. Furthermore, maintenance factors over the subsequent few days and weeks probably impact whether the dissociation is transient and resolves or sets in more permanently.[24] The latter could explain some of the variance in how long after the ingestion the dissociation was noted as present and problematic. The survey revealed that the majority of individuals do not experiment with the culprit drug ever again, highlighting the highly aversive and frightening nature of the experience and its consequences. If the drug was tried again, the survey showed that a negative impact on the depersonalization was predictable and likely. Also of interest, prior lifetime drug use can be quite limited; for example, almost 40% of cannabinoid-triggered cases reported having ingested this widely used recreational drug fewer than 10 times.

The specificity of the drugs that trigger chronic depersonalization unavoidably leads to speculation about the underlying neurochemical systems that subsume the phenomenon. These have been extensively reviewed and summarized elsewhere[29] and are more briefly described here. Cannabis has been experimentally shown to induce depersonalization in healthy volunteers, with a pronounced component of temporal disintegration, and particular brain regions have been implicated.[30] In addition to acting as a partial agonist at presynaptic CB1 receptors, inhibiting γ-aminobutyric acid (GABA)-ergic and enhancing dopaminergic transmission as may be relevant to psychosis,[31] cannabinoids also block *N*-methyl-d-aspartate (NMDA)

receptors at sites distinct from other noncompetitive NMDA antagonists,[32] and therefore their dissociative effect may be partly via NMDA antagonism. Hallucinogens act as agonists at serotonin 5-HT_{2A} and especially 5-HT_{2C} receptors, and experimental challenge studies with the partial 5-HT_{2A} and C agonist *m*-CPP have demonstrated the induction of depersonalization in a mixed group of social phobia, borderline personality disorder, and obsessive-compulsive disorder participants[33]; the induction of flashbacks and dissociative symptoms in a subgroup of posttraumatic stress disorder patients[34]; and the induction of dissociation in healthy volunteers.[35] The NMDA antagonist ketamine, also known as the "dissociative anesthetic" and as the street drug "Special K," induces a profound dissociative state in healthy subjects that has been likened to, but is thought to be partly distinct in the implicated brain pathways, from the psychotomimetic effects of ketamine.[36,37] NMDA receptors are widely distributed in the cortex, hippocampus, and amygdala and mediate associative processes. The precipitation of chronic depersonalization by the selective κ opioid agonist salvia in a few individuals is a novel and interesting finding, to our knowledge, not previously reported; salvia is known to induce acute depersonalization in some individuals. This may be important to note, as salvia is becoming an increasingly popular recreational drug. In one experimental study of healthy volunteers, a placebo-controlled pharmacologic challenge with the κ opioid agonist enadoline induced a "clean" depersonalization-like syndrome with perceptual disturbances and a sense of detachment, in the absence of prominent mood, anxiety, or psychotomimetic effects.[38]

Comparison of the drug- and non–drug-triggered groups revealed very few differences. Similar to a prior report,[10] there was a preponderance of younger and male participants in the drug group, attributable to the demographics of substance use. The nondrug group reported earlier onset by about 2 years, which could be attributable to psychological stressors occurring in childhood and adolescence, as previously reported,[39] earlier than substance use. The longer syndrome duration in the nondrug group may just reflect the earlier onset combined with older age at participation. The 2 groups were similar in symptom severity, disability, impairment, suicidality, and nonresponse to all types of treatment inquired about. One difference between the 2 groups was the overall greater improvement reported over the course of the disorder in the drug group, which did not appear linked to treatment. Table 4 shows that proportionately more drug group participants became much or very much improved and proportionately fewer became worse or very much worse over time. One explanation for this difference may be that if a substance is responsible for the manifestation of an underlying diathesis, future abstinence may increase the likelihood of remission. On the other hand, psychological stressors can be chronic and less controllable and, even if no longer present, their impact on the psyche may persist.

Widely held but empirically unsubstantiated notions about differences in the phenomenology of chronic depersonalization/derealization triggered by chemical versus psychosocial stressors did not hold up in this large sample. It has often been suggested by patients and clinicians alike that drug-induced CDD may involve more perceptual symptoms, especially visual, and more derealization as opposed to depersonalization. It has also been suggested, using common-sensical reasoning, that because drug-induced cases may be less "psychologically" driven and more "chemically" driven, they may be less likely to impair the core sense of selfhood and its associated symptomatic manifestations (eg, unreality of self). This study employed detailed symptom assessment and clearly showed no differences in phenomenology between the 2 groups in any domain, strongly supporting the unity of the syndrome. The only phenomenological difference was greater numbing in the nondrug group ($P = .009$), which, however, was no longer present when controlling for gender. One possible explanation for this finding could be the greater proportion of female subjects in the nondrug group, with possibly greater traumatic stress histories or depression and associated numbness. It cannot, however, be ruled out that this could represent a "true" difference between the 2 groups, with greater numbing being an integral part of a chronic depersonalization syndrome related to psychological stressors.

How then can this uniform syndrome be conceptualized in terms of its pathogenesis? As for other psychiatric disorders, a diathesis × stress model needs to be investigated in future studies, incorporating a pronounced dissociative diathesis at one end of a continuum, in which isolated chemical or more minor psychological triggers suffice to manifest the phenotype, to a strongly environmentally driven expression at the other end, which could be associated with more impressive traumatic stress histories even in the face of lesser diathesis.

There are several limitations to this study. Its survey nature precluded diagnostics for both dissociative and other Axis I disorders. In addition, mood and anxiety symptoms were not inquired about. Even though the very chronic nature of the syndrome in this survey, an average of 10 years, renders it quite unlikely it was occurring exclusively in the context of a mood or anxiety episode (which would rule out a DPD diagnosis according to the *DSM-IV-TR*), this possibility cannot be excluded for all subjects. Similarly, organic etiologies are unlikely in this chronic sample, as they would most likely have been detected and treated or would have progressed, but cannot be ruled out. The survey is retrospective in nature, and thus there could be inaccuracies in the remote drug histories reported by participants. Finally, due to time limitations, the survey did not inquire about other areas of particular interest such as stress and trauma histories. Despite its limitations, the study firmly establishes the major illicit drug culprits in chronic depersonalization, the chronicity and morbidity of the syndrome in the absence of

continued use, limited responsiveness of chronic depersonalization to traditional treatments, and the largely uniform phenotype of the syndrome regardless of antecedent. Future research directions should aim at continued exploration of the implicated neurochemical systems in hope of developing more effective interventions.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), ketamine (Ketalar and others), lithium (Eskalith, Lithobid, and others), methamphetamine (Desoxyn), mirtazapine (Remeron and others).

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Financial disclosure: None reported.

Funding/support: None reported.

Acknowledgment: The authors acknowledge the assistance of the nonprofit organization and Web site of the National Organization for Drug-Induced Disorders (NODID) for collaborating on this study and hosting the current survey (www.nodid.org); the authors also thank the Depersonalization Support Community Web site (www.dpselfhelp.com) for promoting the survey.

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