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Cannabis Withdrawal is Common among Treatment-Seeking Adolescents with Cannabis Dependence and Major Depression, and is Associated with Rapid Relapse to Dependence

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Abstract

Recently, reports have suggested that cannabis withdrawal occurs commonly in adults with cannabis dependence, though it is unclear whether this extends to those with comorbid depression or to comorbid adolescents. We hypothesized that cannabis withdrawal would be common among our sample of comorbid adolescents and young adults, and that the presence of cannabis withdrawal symptoms would be associated with a self-reported past history of rapid reinstatement of cannabis dependence symptoms (rapid relapse). The participants in this study included 170 adolescents and young adults, including 104 with cannabis dependence, 32 with cannabis abuse, and 34 with cannabis use without dependence or abuse. All of these subjects demonstrated current depressive symptoms and cannabis use, and most demonstrated current DSM-IV major depressive disorder and current comorbid cannabis dependence. These subjects had presented for treatment for either of two double-blind, placebo-controlled trials involving fluoxetine. Cannabis withdrawal was the most commonly reported cannabis dependence criterion among the 104 subjects in our sample with cannabis dependence, being noted in 92% of subjects, using a two-symptom cutoff for determination of cannabis withdrawal. The most common withdrawal symptoms among those with cannabis dependence were craving (82%), irritability (76%), restlessness (58%), anxiety (55%), and depression (52%). Cannabis withdrawal symptoms (in the N=170 sample) were reported to have been associated with rapid reinstatement of cannabis dependence symptoms (rapid relapse). These findings suggest that cannabis withdrawal should be included as a diagnosis in the upcoming DSM-V, and should be listed in the upcoming criteria list for the DSM-V diagnostic category of cannabis dependence.

1. Introduction

The current version of the DSM, the DSM-IV-TR, acknowledges that “There is some evidence that a majority of chronic users of cannabinoids report histories of tolerance or withdrawal…” (American Psychiatric Association, 2000, p. 236). The DSM-IV-TR (p. 235) also states that “Symptoms of possible cannabis withdrawal (e.g., irritable or anxious mood

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accompanied by physiological changes such as tremor, perspiration, nausea, change in appetite, and sleep disturbances) have been described in association with the use of very high doses, but their clinical significance is uncertain. For these reasons, the diagnosis of cannabis withdrawal is not included in this manual." For similar reasons, cannabis withdrawal was not accepted as one of the diagnostic criteria for cannabis dependence in the DSM-IV-TR. However, some recent authors have suggested that cannabis dependence should be accepted as a diagnosis and as a diagnostic criterion for cannabis dependence in the upcoming DSM-V (Budney, 2007; Crowley, 2007), while others have concluded that studies conducted to date do not provide strong evidence base for the existence of a cannabis withdrawal syndrome in human users (Smith, 2002). In contrast to the DSM-IV, the International Classification of Diseases (ICD) recognizes a cannabis withdrawal syndrome, but states that its diagnostic criteria remain to be determined (World Health Organization, 2007).

Several recent papers have described marijuana withdrawal among humans, and indeed have found that withdrawal symptoms are present in the majority of chronic heavy cannabis users (Crowley et al, 1998; Budney et al, 1999; Budney et al., 2003; Budney et al., 2004; Vandrey et al, 2005; Crowley, 2007). Studies involving clinical samples of adults seeking treatment for cannabis abuse or dependence showed even higher rates of cannabis withdrawal than studies conducted among community populations. For example, a recent review showed that across studies, 51–95% of the adults seeking treatment for cannabis abuse or dependence reported cannabis withdrawal during the past year (Budney, 2007). Proponents of including cannabis withdrawal have recently provided evidence regarding its typical onset (2 days after cessation of use) and duration (7–14 days) (Budney et al, 2003). Proponents have shown that common symptoms of cannabis withdrawal are primarily emotional and behavioral (Budney et al, 2004; Vandrey et al, 2005), and do not include the significant medical or physical symptoms sometimes observed with opioid, sedative, or alcohol withdrawal (Budney et al, 2003). Kouri & Pope (2000) have shown that anxiety, irritability, physical symptoms, tension, decreased mood, and decreased appetite are noted among those with cannabis withdrawal compared to controls during a 28-day period of supervised abstinence. Dawes and colleagues (2006) have demonstrated cannabis withdrawal among adolescent cannabis users in an outpatient research setting. In addition, laboratory studies have demonstrated cannabis withdrawal symptoms across multiple nonhuman species (Budney et al., 2004).

Recent studies have also shown that withdrawal symptoms abate with re-administration of cannabis, are due to deprivation of a specific substance (cannabis), and are clinically significant (Crowley et al., 1998; Coffey et al., 2002; Budney et al., 2004). Similarly, 38% of adolescents with cannabis dependence reported that they used cannabis to avoid withdrawal symptoms (Coffey et al, 2002). Thus, cannabis withdrawal may precipitate a more rapid return to heavy use following a period of abstinence. In addition, cannabis withdrawal may be a mechanism underlying a stereotyped pattern of use of cannabis; that is, highly regulated use of cannabis to minimize withdrawal effects.

Less information is available on cannabis withdrawal among adolescents as compared to among adults (Vandrey et al., 2005). The majority of individuals who use marijuana or who have a cannabis use disorder are adolescents or young adults (Compton et al, 2004). Recent data suggest that 47% to 67% of adolescents with cannabis dependence report cannabis withdrawal (Crowley, 2007). Data regarding comorbid adolescent populations are particularly scarce.

While there is little doubt that cannabis withdrawal occurs, the nature of the association of cannabis withdrawal symptoms and comorbid disorders is unclear. To date, the potential effects of psychiatric comorbidity on level of cannabis withdrawal symptoms remain largely unexplored. In this study, we examined the symptom profile and symptom prevalence of

adolescents with comorbid cannabis dependence and major depressive disorder. To our knowledge, this is the first study to examine those clinical features among any population of adolescents and young adults with cannabis dependence and a comorbid psychiatric disorder (major depressive disorder). Our first aim was to determine the prevalence of cannabis withdrawal among adolescents with comorbid cannabis dependence and major depressive disorder. We hypothesized that cannabis withdrawal symptoms would be common (present in over half) in our comorbid adolescent population with cannabis dependence. We also hypothesized that the presence of cannabis withdrawal symptoms would be associated with rapid reinstatement of cannabis dependence symptoms (rapid relapse).

2. Method

2.1 Procedures

This study was conducted in a research clinic focusing on comorbid youth at the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, Pennsylvania. All patients were recruited from radio and newspaper advertisements, posters, and outpatient clinics. None of the subjects described in this report were recruited from an inpatient unit. All subjects were first screened by telephone to ensure that they complained of current (last week) depressive symptoms and cannabis use, and to ensure that they were within the age range for participation. Before entry into the protocol, written informed consent was obtained after all procedures had been fully explained. The study was approved by the University of Pittsburgh Institutional Review Board. The participants in this study consisted of 170 adolescents and young adults who had presented for treatment in either of two similar double-blind, placebo-controlled federally funded medication trials, both of which involved the comparison of fluoxetine (20 mg) versus placebo among comorbid adolescents. The first of those two treatment studies (R01 DA19142) (N=78) (Principal Investigator=JRC) was designed to assess the efficacy of fluoxetine (20mg) versus placebo for treating adolescents and young adults (age 14–25) with cannabis dependence and major depressive disorder. The second of those two treatment studies (R01 AA13370) (N=92) (Principal Investigator=JRC) was designed to assess the efficacy of fluoxetine (20mg) for treating adolescents (age 15–20) with an alcohol use disorder and major depressive disorder, though many of those persons also met diagnostic criteria for cannabis abuse or dependence. To date, those two treatment studies remain ongoing, so the medication blind has not been broken, and no outcome findings are available. However, brief descriptions of these two studies have recently been published (Cornelius, Clark, et al, 2005; Lamberg, 2007). The findings described in this paper were all taken from baseline assessments, so the results of the medication blind were not needed in order to conduct the analyses for this paper.

Inclusion and exclusion criteria were similar across the two studies. For the first study, inclusion criteria included a current DSM-IV (SCID) diagnosis of cannabis dependence or cannabis abuse and a current DSM-IV (KSADS) diagnosis of major depressive disorder (MDD), and a Hamilton Depression (HAM-D-24) score or Beck Depression Inventory (BDI) score of greater than or equal to 15 (in order to ensure adequate current depressive symptoms). Alcohol abuse, alcohol dependence, and nicotine dependence were not exclusion criteria for the first study, and indeed most of the subjects in that study also exhibited alcohol dependence or alcohol abuse. For the second study, inclusion criteria included a current DSM-IV (SCID) diagnosis of alcohol dependence or alcohol abuse, a current DSM-IV (KSADS) diagnosis of MDD, and a HAM-D-24 or Beck Depression Inventory (BDI) depression rating score of greater than or equal to 15. Cannabis dependence was not an exclusion criterion for the second study, and indeed most of the subjects in that study also exhibited cannabis dependence. Subjects from the second study were included in the analyses currently being reported only if they demonstrated a cannabis use disorder and/or cannabis use in addition to their alcohol use disorder. The analyses presented in this paper include baseline data from subjects who were

included in the subsequent treatment trials and those who were excluded from participation in the subsequent treatment trials after completion of their informed consent and baseline assessment.

The other exclusion criteria were the same for both treatment studies, and included the presence of bipolar disorder, schizoaffective disorder, schizophrenia, hyper-or hypothyroidism, significant cardiac, neurological, or renal impairment, and those with significant liver disease (SGOT, SGPT, or gamma GTP greater than 3 times normal levels). Potential subjects were also excluded from both studies if they had received psychotropic medication within the three months before the baseline assessment. Both studies excluded potential subjects if they demonstrated a DSM-IV dependence diagnosis involving any substance except cannabis, alcohol, or nicotine. Persons with a history of a serious suicide attempt, those who had used any form of intravenous drugs, or those who had demonstrated significant medication side effects on fluoxetine in the past were also excluded from both studies. Other exclusion criteria for both studies included pregnancy, inability or unwillingness to use contraceptive methods, and an inability to read or understand study forms.

The baseline assessment was thorough, and typically required a total of about five hours for completion. The baseline assessment was conducted in two parts, including a three-hour initial session and a subsequent two-hour additional session. All subjects in both treatment studies completed a comprehensive medical examination and laboratory tests prior to entering the study. All female participants completed a urine pregnancy test prior to participation in either study. All subjects in both studies completed a urine drug screen and a breathalyzer prior to participation in the studies.

2.2 Measures

The SCID substance use disorder instrument used in these studies was adapted for use with adolescents and young adults, and has good inter-rater and concurrent validity (Martin et al., 2000). This adapted SCID included an item querying cannabis withdrawal, as indicated by 22 possible symptoms (Budney et al., 1999; Budney et al., 2004). Two different thresholds were used to define cannabis withdrawal in the current manuscript, including a 2-symptom cut-off and a 4-symptom cut-off used in previous research. The 2-symptom cut-off, which was the primary cut-off used in our study, was based on the work of Weisbeck et al. (1996), while the 4-symptom cut-off was based on the work of Budney et al. (1996) and of Vandrey et al. (2005). Due to co-occurring major depression in many subjects, the masters-degree level assessors for this study were trained to probe whether withdrawal symptoms that may be related to mood (e.g. irritability, insomnia) represented either new onset or an exacerbation of existing mood symptoms to clarify the presence of clinically significant withdrawal in the presence of co-occurring depression. Only those symptoms that had their onset with cannabis abstinence or that clearly increased in severity with cannabis abstinence were included as withdrawal symptoms.

Some additional considerations are worth noting regarding the source of withdrawal symptoms among the subjects in the study currently being reported. First, it is noteworthy that persons with substance use disorders other than cannabis dependence, alcohol dependence, or nicotine dependence were excluded from the study, so other substance could not have contributed to withdrawal symptoms. Since the subjects were all young, they did not have the symptoms of alcohol withdrawal which typify alcohol dependence in adults. For example, none of the subjects in the study had ever exhibited delirium tremens (DTs), blackouts, or withdrawal seizures. Also, none of the subjects drank every day of the week, but instead typically only drank alcohol on weekends, as is typical of adolescents. None of the subjects required detoxification from alcohol prior to their participation in a treatment study. Indeed, none of the subjects exhibited alcohol withdrawal symptoms that lead the investigators to even consider

detoxification from alcohol in any of the subjects. Similarly, the levels of cigarette smoking were typically low, and usually did not occur every day of the week, so withdrawal symptoms from nicotine were minimal to absent. Also, the time course of use of cannabis was also substantially different from that of cigarette or alcohol use, which facilitated the distinction of withdrawal from cannabis versus withdrawal from nicotine or alcohol.

The SCID also included exploratory items on Rapid Reinstatement of Dependence Symptoms following a one-month or greater period of abstinence (rapid relapse) (Martin et al., 2000). Rapid Reinstatement of Dependence (rapid relapse) was defined as a return to at least two previously presenting dependence symptoms within one month of use following a one-month or greater period of abstinence. Because this study was conducted with cross-sectional data rather than longitudinal data, Rapid Reinstatement of Dependence (rapid relapse) was based on the subjects' unverified retrospective self-reports.

2.3 Statistical methods

A list of the prevalence of the various DSM-IV cannabis dependence criteria was constructed (Table 1), and the prevalence of these criteria was compared across those with those with cannabis dependence, cannabis abuse, and cannabis use without either cannabis abuse or dependence. Thereafter, a list of the prevalence of specific cannabis withdrawal symptoms was constructed (Table 2), and the prevalence of those symptoms was compared across the same three subject groups.

Thereafter, the chi-square test was used to determine whether the presence of cannabis withdrawal symptoms (at a 2- or 4-symptom threshold for defining cannabis withdrawal) was associated with Rapid Reinstatement of Cannabis Dependence Symptoms (rapid relapse). These chi-square tests included data from all 170 of the subjects, including those with cannabis dependence, cannabis abuse, and current cannabis use. These other non-cannabis dependence comparison groups were included in those analyses in order to provide a broader spectrum of severity of cannabis-related problems.

3. Results

3.1 Sample

The total sample consisted of a total of 170 subjects. These 170 subjects consisted of persons with cannabis dependence or cannabis abuse or cannabis use in combination with current depressive symptoms, most of whom (N=125) were found to demonstrate major depressive disorder. These 170 subjects included persons with current cannabis dependence (N=104) who are described in greater detail in the paragraph immediately below, but also included persons who demonstrated cannabis abuse (N=18), "diagnostic orphans" (N=14) (one or two diagnostic criteria for dependence, but without meeting criteria for either abuse or dependence) (Pollock & Martin, 1999), and N=34 persons with cannabis use but no current DSM criteria of cannabis abuse or dependence. These other non-cannabis dependence comparison groups were included in those analyses in order to provide a broader spectrum of severity of cannabis-related problems. Those 170 subjects included 92 males (54.1%) and 78 females (45.9%), including 120 Caucasians (70.6%) and 39 African-Americans (22.9%), 1 American Indian (0.6%), 2 Asian-Americans (1.2%), and 8 multiple-race subjects (4.7%). The age of this group was 20.3 years +/− 2.1 years. The analyses involving Rapid Reinstatement of Cannabis Dependence included the entire (N=170) study sample in order to include a wider range of cannabis-related clinical presentations. Cannabis use occurred a mean of 14.6 +/− 11.5 times/month among these participants. The strong majority of the subjects (greater than 90%) had not received treatment for depression prior to their baseline assessment as part of the study currently being

reported. That observation reflects the fact that the subjects were young, and were typically in their first episode of major depression.

3.2 Associations with cannabis withdrawal in the entire (N=170) sample

In analyses involving the entire (N=170) sample, the number of cannabis withdrawal symptoms was found to be significantly higher in the cannabis dependence group than among those with cannabis abuse or the "diagnostic orphans" (those who demonstrated one or two symptoms of dependence with no symptoms of abuse) or compared to those with current cannabis use but without cannabis dependence or abuse (mean=6.0 vs mean=3.1 vs mean=0.5, respectively, F=39.1, df=2,166, p=0.000). In that sample, cannabis withdrawal was found to be associated with rapid relapse using the 2 withdrawal symptom cut-off to define the presence of cannabis withdrawal (chi-square=10.8, df=1, p=0.001) and also using the 4 withdrawal symptom cut-off (chi-square=8.9, df=1, p=0.003).

3.3 Characterizing cannabis withdrawal in subjects with cannabis dependence and a depressive disorder

The study sample used to characterize cannabis withdrawal among those with cannabis dependence did not include the entire sample, but rather only included those 104 subjects who demonstrated cannabis dependence. Subjects who exhibited cannabis abuse or who exhibited cannabis use without dependence or abuse were excluded from those analyses. The subjects with cannabis dependence in this study included 53 males (51.0%) and 51 females (49.0%). These subjects included 68 Caucasian, 29 African-American, 6 multiracial, and 1 Asian participants, ranging from 14 to 25 years of age (mean 20.6 +/− 2.3 years). These participants met an average of 5.0 +/− 1.1 lifetime DSM-IV diagnostic criteria for cannabis dependence. Most (N=80) of those subjects also demonstrated a current diagnosis of major depressive disorder, and a larger number (N=85) demonstrated a lifetime diagnosis of major depressive disorder. Cannabis use occurred a mean of 19.6 +/− 10.0 times/month among these participants. The mean number of cannabis withdrawal symptoms in this cannabis dependent group was 6.0 +/− 3.6. The mean self-rated Beck Depression Inventory Score in this group was 20.6 +/− 9.2, and the mean Hamilton Depression score was 16.1 +/− 8.7.

The most commonly reported cannabis dependence criterion reported by those with cannabis dependence (N=104) was withdrawal, which was reported by 95 subjects (91% of subjects, using a two-symptom cutoff, or 73% of subjects, using a four-symptom cutoff). All of the other cannabis dependence criteria were also commonly reported, and were reported by about half of the population or more (see table 1).

The prevalence of various specific withdrawal symptoms reported by those with cannabis dependence (N=104) (from the list of 22 possible withdrawal symptoms) is listed on table 2. The most common symptoms in that list were craving cannabis, irritability, restlessness, anxiety, and depressed mood, respectively, all of which were reported by at least half of the sample. Most somatic symptoms were reported only rarely.

4. Discussion

This study provides what we believe is the first data regarding cannabis withdrawal from adolescents and young adults with comorbid cannabis dependence and major depressive disorder. Our first hypothesis was confirmed, in that cannabis withdrawal was found to be common in our youthful comorbid population with cannabis dependence and comorbid major depressive disorder. Indeed, cannabis withdrawal at a 2-symptom threshold was the most commonly reported cannabis dependence criterion, and was the third most commonly reported cannabis dependence criterion at a 4-symptom threshold. These findings are consistent with

other recent findings concerning the common occurrence of withdrawal symptoms among those with cannabis use disorders (Crowley, 2007; Budney, 2007).

The most commonly reported specific withdrawal symptoms were cannabis craving, irritability, restlessness, anxiety, and depression. These findings are consistent with the reports of Budney et al., 2004, and of Vandrey et al., 2005, that common symptoms of cannabis withdrawal are primarily emotional and behavioral, and not the medical or physical symptoms sometimes observed with opioid, sedative, or alcohol withdrawal. The number of cannabis withdrawal symptoms was found to be significantly higher in the cannabis dependence group than among the two comparison groups with either cannabis abuse or in those with cannabis use but without cannabis abuse or dependence. We found that the presence of cannabis withdrawal symptoms was associated with rapid reinstatement of cannabis dependence symptoms (rapid relapse), as had been hypothesized. This additional finding provides evidence to support the clinical significance of cannabis withdrawal symptoms in the clinical course of adolescents and young adults with cannabis dependence.

These findings concerning the prevalence and clinical correlates of cannabis dependence suggest that the cannabis withdrawal syndrome should be included in the upcoming DSM-V, and also suggest that cannabis withdrawal should be included as one of the diagnostic criteria for cannabis dependence. Currently, in the DSM-IV and ICD-10, withdrawal is a dependence criterion for every substance except cannabis and hallucinogens (Hasin et al, 2007). Both of those suggestions have recently been made by other recent researchers in the field (Crowley, 2007; Budney, 2007). Thus, our current findings and suggestions reinforce those of other researchers in the field, and extend the cannabis withdrawal findings to comorbid adolescents with cannabis dependence in combination with major depression. Specifically, we concur with the conclusion of Crowley (2007), who stated that “Given the weight of evidence now supporting the clinical significance of a cannabis withdrawal syndrome, the burden of proof must rest with those who would exclude the syndrome from DSM-V.”

Our current study is limited by its moderate sample size, the use of only a single recruitment site, and the use of cross-sectional data. Also, since the current study involved a young sample, the results may not generalize to older adults. In addition, it should be noted that type I statistical error might have been a problem for some of the comparisons because of multiple statistical comparisons, though most of the findings reported as statistically significant were robust in magnitude. Future research is warranted to determine the optimal algorithm for diagnosing cannabis withdrawal (Martin et al., 2006; Schuckit & Saunders, 2007). In addition, future research is warranted to determine whether the cannabis dependence criteria need to be modified in adolescents, as compared to those used with adults (Schuckit & Saunders, 2007). Further study is also needed to better understand the role of depression in sensitivity to and possible exacerbation of cannabis withdrawal symptoms and in relapse to cannabis use following treatment (Cornelius et al., 1999; Cornelius, Clark, Bukstein, & Salloum, 2005). Finally, future longitudinal follow-up studies are warranted to clarify the role of cannabis withdrawal symptoms in precipitating cannabis relapse.

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Table 1

Prevalence of the various DSM-IV cannabis dependence criteria (total *n*=170)

Criterion	Cannabis Dependence n=104	%	Cannabis Abuse n=32	%	Cannabis Use n=34	%	Chi-square	df	p
1. Tolerance	91	87.5	15	46.9	5	14.5	65.8	2	0.000
2. Withdrawal	95	91.3	18	56.3	4	11.8	78.5	2	0.000
3. Larger/Longer Use	79	76.0	5	15.6	2	5.9	69.6	2	0.000
4. Unsuccessful attempts to cut down/quit	62	59.6	5	15.6	4	11.8	35.2	2	0.000
5. Time Spent	90	86.5	18	56.3	5	14.7	61.2	2	0.000
6. Work/Social Obligations	54	51.9	0	0.0	2	5.9	44.0	2	0.000
7. Physical/Psychological Symptoms	51	49.0	4	12.5	2	5.9	29.2	2	0.000

Table 2

Prevalence of the various cannabis withdrawal symptoms (from list of 22)
These symptoms must increase during abstinence in order to be counted as positive

Symptom	Cannabis Dependence n=104	%	Cannabis Abuse n=32	%	Cannabis Use n=34	%	Chi-Square	df	p
Craving cannabis	84	81.6	16	50.0	3	8.8	58.8	2	0.000
Irritability	78	75.7	13	40.6	3	8.8	50.0	2	0.000
Restlessness	60	58.3	12	37.5	2	5.9	29.1	2	0.000
Anxiety	57	55.3	10	31.3	1	2.9	30.5	2	0.000
Depression	54	52.4	6	18.8	2	5.9	29.3	2	0.000
Change in appetite	47	45.6	4	12.5	1	2.9	28.1	2	0.000
Trouble sleeping	45	43.7	8	25.0	1	2.9	20.4	2	0.000
Trouble concentrating	41	39.8	5	15.6	2	5.9	17.6	2	0.000
Tiredness, drowsiness, weakness	28	27.2	3	9.4	1	2.9	12.1	2	0.002
Anger, violent outbursts	28	27.2	5	15.6	1	2.9	9.8	2	0.007
Headache	27	26.2	6	18.8	0	0.0	11.2	2	0.004
Yawning	22	21.4	6	18.8	0	0.0	8.6	2	0.014
Vivid unpleasant dreams	16	15.5	1	3.1	0	0.0	8.9	2	0.012
Fast heartbeat	7	6.8	1	3.1	0	0.0	2.8	2	0.241
Tremor or twitch	6	5.8	2	6.3	0	0.0	2.1	2	0.346
Nausea or vomiting	5	4.9	0	0.0	0	0.0	3.3	2	0.192
Watery eyes or runny nose	5	4.9	0	0.0	0	0.0	3.3	2	0.192
Diarrhea or upset stomach	4	3.9	0	0.0	0	0.0	2.6	2	0.269
See, hear or feel things	4	3.9	1	3.1	0	0.0	1.3	2	0.510
Muscle pain	4	3.9	0	0.0	0	0.0	2.6	2	0.269
Sweats or fever	1	1.0	0	0.0	0	0.0	0.6	2	0.724
Seizures	0	0.0	0	0.0	0	0.0	-	-	-