

# Pattern and Risk Factors of Alcohol Withdrawal Delirium

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**Objective:** To determine the incidence, prescribing risk factors of alcohol withdrawal delirium (AWD), and factors complicating AWD, in alcohol dependent patients hospitalized for alcohol detoxification.

**Material and Method:** Patients attending the detoxification program at Chiang Mai University Hospital and the Northern drug dependence treatment center between May and September 2005 were assessed. Patients with signs of AWD at baseline were excluded. Incidence, risk factors, and dosage of benzodiazepines of patients with and without subsequent AWD were compared. Risk factors that prolonged the course of AWD were analyzed.

**Results:** Nineteen male patients were assessed. Ten patients (52.6%) developed AWD despite receiving benzodiazepine detoxification. Risk factors of age, previous history of AWD and epilepsy, alcohol use history, frequency and quantity of drinking, signs of simple withdrawal at first admission, and dosage of benzodiazepines were not significantly different between the groups. However, patients with systolic blood pressure at first admission ( $> 120$  mmHg) had longer duration of AWD than those without abnormal blood pressure ( $72.0 \pm 53.7$  hr versus  $168.0 \pm 24.0$  hr, respectively,  $p = 0.038$ ).

**Conclusion:** The incidence of AWD was relatively high despite treatment. Although the present study did not find any risk factor predicting AWD. AWD patients hypertensive at the first admission had significantly longer duration of delirium. Physicians should be aware of, monitor and treat hypertensive state and give early treatment of alcohol withdrawal with adequate doses of benzodiazepines to decrease morbidity and mortality of AWD.

**Keywords:** Alcohol withdrawal delirium, Pattern, Risk factors

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Alcohol dependence and alcohol withdrawal delirium are common and costly, representing one of the most prevalent psychiatric and medical conditions, as well as causes of death in Thailand<sup>(1-5)</sup>. AWD or delirium tremens (DTs), which is the most common complication of alcohol withdrawal, usually occurs within 48-72 hours after alcohol cessation or reduction. AWD occurred in 0-48.5% of patients who received treatment of alcohol withdrawal<sup>(6-10)</sup> and mortality from AWD was 15%<sup>(8)</sup>. All patients with this condition should be hospitalized and treated with psychotropic drugs (e.g., benzodiazepines) to improve the disturbance of neurotransmitter systems, decrease the symptoms and prevent morbidity, and mortality. Meta-analysis shows that benzodiazepines (BZDs) possess better efficacy than antipsychotics and anticonvulsants, a greater margin of safety and have widespread use

for the treatment of alcohol withdrawal, with the goals of reducing agitation, the severity of withdrawal and preventing delirium<sup>(11)</sup>. However, some patients developed AWD despite receiving a detoxification program<sup>(7-10)</sup>.

Study of alcohol withdrawal delirium has increased rapidly in Western countries. In Thailand, there are a few research projects about alcohol-use disorder, risk factors and intervention models to stop drinking<sup>(12-14)</sup>. Even though in clinical practice there are many detoxification centers in Thailand, limited data are available about prevalence or incidence, pattern, and risk factors of AWD in detoxification centers.

The present study was an observational prospective study to assess the incidence, pattern, risk and factors that prolong the course of AWD in Thai alcohol dependent patients who have no symptoms of AWD and were voluntarily hospitalized for alcohol detoxification.

## Material and Method

This was an 8-day, observational prospective study to assess the incidence of AWD of inpatients

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aged from 18 to 65 years with a current diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition<sup>(15)</sup> between May and September 2005. Patients were recruited from two investigational sites in Chiang Mai, at Chiang Mai University Hospital and the other site at the Northern drug dependence treatment center. Male and female inpatients were eligible for study entry if they were hospitalized for alcohol detoxification. Patients were excluded if they presented with any sign of complicated AWD before being admitted or had stopped drinking alcohol for more than five days.

The present study assessed five domains, the demographic data, pattern of alcohol consumption, vital sign and signs of simple withdrawal at the first admission, the severity of alcohol withdrawal syndrome, onset, and duration of delirium and dosage of BDZs that patients received. Firstly, the researchers recorded the demographic data including age, sex, history of illicit drug use, physical and psychiatric illness, history of seizure, AWD and complications associated with alcohol withdrawal syndrome. Then, the researchers evaluated the pattern of alcohol consumption such as age of onset of drinking; duration of drinking [total time (years) of continuous use alcohol], duration of abstinence [time that the patient can stop drinking for more than 1 month], frequency of drinking (days of drinking per week) during past three months and one week before admission and quantity of drinking during the past three months and one week before admission [daily units of alcohol intake, 1 unit (U) contains approximately 10 gram of ethyl alcohol]. Afterwards, the researchers assessed vital sign and signs of simple withdrawal at the first admission. Subsequently, the researchers monitored the severity of alcohol withdrawal syndrome by using the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale<sup>(16)</sup>, which is a validated 10-items assessment tool including nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache, or fullness in head and orientation. The maximum score is 67. Lower scores (< 9) correspond to mild withdrawal, scores of 9 to 15 points correspond to moderate withdrawal and scores of greater than 15 points correspond to severe withdrawal symptoms and an increased risk of delirium tremens and seizures. Moreover, patients who developed delirium had diagnostic confirmation with the Confusion Assessment Method for

the Intensive Care Unit (CAM-ICU)<sup>(17)</sup>, a 2-minute assessment instrument, demonstrated a sensitivity of 93% to 100%, with a specificity of 98% to 100%, and high inter-rater reliability in the detection of delirium. CAM-ICU assessed all four features, 1-an acute onset of changes or fluctuations in the course of mental status, 2-inattention, 3-disorganized thinking and 4-an altered level of consciousness (*i.e.*, other than alert). The patients were diagnosed with delirium (*i.e.*, CAM positive) if they presented both features 1 and 2, plus either feature 3 or 4. From daily assessment, scores from both tools could show the clinical presentation pattern of any AWD. If the patients developed delirium, the researcher would record onset, duration and dosage of BDZs (equivalence dose of diazepam) to explore the potential factors that might prolong the course of AWD. All patients were treated with fixed-schedule doses of benzodiazepine and decreasing doses during the treatment period. Additional doses were only given when considered necessary. However, the assessors were blinded and not treating the patients.

Statistical analysis was carried out using SPSS for Windows evaluation version 17.0. The data were analyzed to find the difference between the groups of participants with and without AWD. Descriptive methods (*e.g.*, frequencies and percentages or mean  $\pm$  SD) were used to present the demographic and clinical features of the patients. In addition, the mean differences between AWD and associated factors were analyzed by using the Chi-square test or the Mann-Whitney U test. All calculated p-values were 2 sided, statistical significance was set at  $p < 0.05$ . Patients with and without delirium were compared for onset, duration and factors that prolong course of AWD.

The present study was approved by the Ethics Committee of Chiang Mai University, and all patients provided informed consent. None of the patients was paid for their participation in the present study.

## Results

Nineteen patients provided informed consent and were recruited into the present study, of whom 100% met eligibility criteria at baseline and all participants completed the detoxification program. All of the participants were men. The mean age was  $42.8 \pm 8.5$  years, the mean age at onset of drinking was  $18.0 \pm 4.2$  years, and their mean duration of drinking was  $24.8 \pm 9.1$  years. The mean number of times

participants could stop drinking for longer than one month was  $2.3 \pm 4.5$  times. All patients did not recently use illegal substances. The demographic data, pattern of alcohol consumption, and signs of simple withdrawal at first admission are presented in Table 1. Regarding clinical variables, there were no differences between the two groups in respect of risk factors of AWD such as age, previous history of AWD and epilepsy, alcohol use history, frequency and quantity of drinking and signs of simple withdrawal at first admission as in Table 1.

The incidence of AWD was 52.6% (10/19). Mean onset and duration of delirium were  $14.4 \pm 16.8$  hr (0-48 hr) and  $100.8 \pm 64.8$  hr, respectively. All patients with AWD had higher CIWA-Ar score than patients without AWD within 48.0-72.0 hours after admission but there was no significant difference between CIWA-Ar scores between two groups from d0 to d7 ( $p = 0.90, 0.65, 0.49, 0.84, 0.19, 0.30, 0.34, \text{ and } 0.30$  respectively)\*.

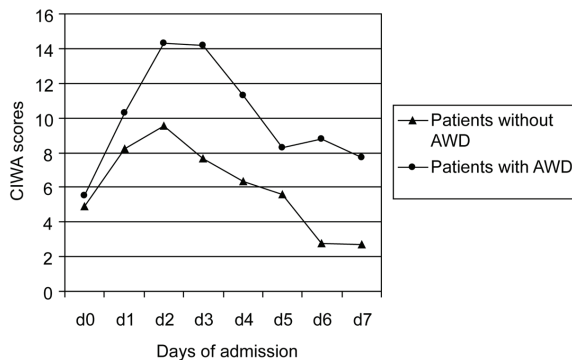
The pattern of alcohol withdrawal syndrome (AWS) of patients with and without AWD from CIWA-Ar scores is shown in Fig. 1. Patients who had CIWA-Ar scores  $> 10$  on the first day after admission showed a trend to develop AWD. Dosages of benzodiazepines used from d0 to d7 in both groups are shown in Fig. 2. There was no significant difference between dosages of BDZs used among the two groups from d0 to d7 ( $p = 0.70, 0.90, 0.93, 0.77, 0.67, 0.68, 0.64, \text{ and } 0.87$  respectively).

As seen in Fig. 3, among those who developed AWD during detoxification, patients with systolic blood pressure more than 120 mmHg had a significantly longer duration of delirium ( $168.0 \pm 24.0$  hr; range 144.0-192.0 hr) than patients with systolic blood pressure equal to or less than 120 mmHg at the time of their first visit ( $72.0 \pm 53.7$  hr; range 24.0-168.0 hr;  $p < 0.005$ ). However, onset and duration of AWD did not vary with other demographic data or other clinical parameters: pattern of alcohol consumption, signs of

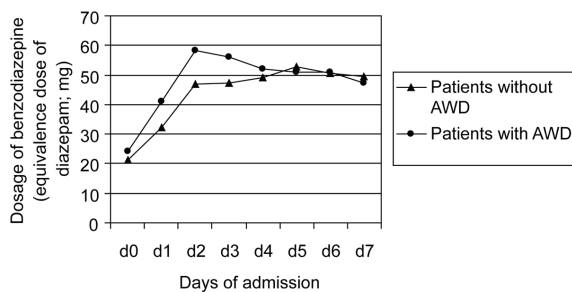
**Table 1.** Demographic and drinking variables at intake of patients

Demographic data	Patients with AWD (n = 10)	Patients without AWD (n = 9)	Statistical test p-value
Age (years)	$44.8 \pm 4.8$	$40.7 \pm 11.2$	0.302
Medical conditions			
Physical illness (%)	40.0 (4/10)	22.2 (2/9)	0.418
Psychiatric illness (%)	20.0 (2/10)	22.2 (2/9)	0.939
History of epileptic seizures (%)	20 (2/10)	22.2 (2/9)	1.000
History of alcohol withdrawal delirious episodes (%)	70 (7/10)	44.4 (4/9)	0.307
History of complicated alcohol withdrawal (%)	60 (6/10)	33.3 (3/9)	0.307
Alcohol use history			
Pattern of alcohol consumption			
Age onset of drinking (years)	$19.0 \pm 5.0$	$16.9 \pm 2.8$	0.510 <sup>a</sup>
Duration of drinking (years)	$25.8 \pm 8.6$	$23.8 \pm 10.0$	0.642
Number of time of abstinence	$3.1 \pm 6.1$	$1.3 \pm 1.6$	0.409
Frequency of drinking			
Days of drinking per week during past 3 month	$6.0 \pm 2.3$	$6.2 \pm 1.2$	0.712
Days of drinking per week (last 7 days)	$6.6 \pm 1.3$	$6.7 \pm 1.0$	1.000
Quantity of drinking			
Daily number of units (U) of alcohol intake during past 3 month	$21.9 \pm 17.0$	$23.7 \pm 13.5$	0.801
Daily number of units (U) of alcohol intake (last 7 days)	$21.2 \pm 13.3$	$24.8 \pm 17.3$	0.613
Total number of drinks (last 7 days)	$146.8 \pm 95.7$	$172.5 \pm 1.2$	0.616 <sup>b</sup>
Signs of simple withdrawal at the first admission			
Sleep problem (%)	40 (4/10)	66.7 (6/9)	0.258
Agitation (%)	70 (7/10)	88.8 (8/9)	0.326
Autonomic abnormality (%)	70 (7/10)	77.8 (7/9)	0.708
Dosage of diazepam (mg per day)	$43.7 \pm 10.0$	$47.6 \pm 17.8$	0.571 <sup>b</sup>
Total dose of diazepam (mg) <sup>c</sup>	$381.0 \pm 142.6$	$350.0 \pm 80.3$	0.571 <sup>b</sup>

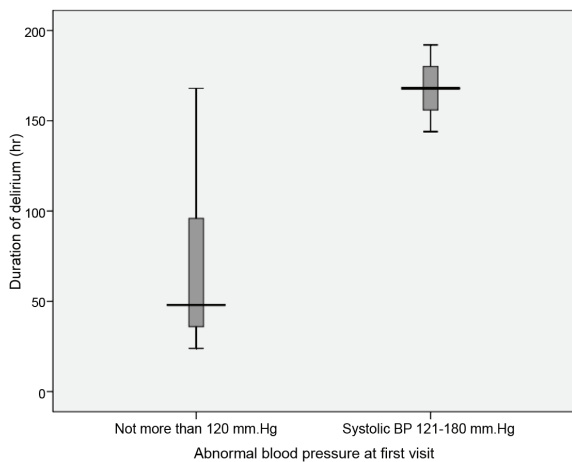
<sup>a</sup> t-test, <sup>b</sup> Fisher's exact test, <sup>c</sup> Mann-Whitney U test  
AWD = alcohol withdrawal delirium



**Fig. 1** CIWA-Ar scores of patients with and without alcohol withdrawal delirium (AWD)



**Fig. 2** Equivalences doses of diazepam (mg) of patients with and without AWD on day 0-7



**Fig. 3** Duration of delirium (hr) among patients with and without BP > 120 mmHg systolic blood pressure at first visit

simple withdrawal at the first admission, previous history of seizure; delirium or complicate alcohol withdrawal syndrome, and co-morbid medical or psychiatric illness.

## Discussion

The result of the present study has allowed the authors to provide a more detailed account of the natural history of AWD in Thailand. The onset of AWD found in the present study ( $14.4 \pm 16.8$  hr) was similar to another study<sup>(8)</sup>. The incidence of AWD in the present study was higher than other studies<sup>(6-10)</sup>. This high incidence of AWD may be attributed to a relatively low dose of benzodiazepine in the first three days of detoxification. From the present study, patients with and without AWD received the same equivalent dose of diazepam during the detoxification. At risk groups for AWD-should be closely monitored in the critical period of potential change from simple alcohol withdrawal to alcohol withdrawal delirium<sup>(6)</sup> and promptly treated with adequate doses of benzodiazepine to prevent the symptoms of AWD<sup>(6-8)</sup>. However, patients with AWD in the present study received a relatively low dose of benzodiazepine in the first three days of detoxification compared with other studies<sup>(6-8)</sup>.

Other research<sup>(7,9,10)</sup> found risk factors of AWD such as prior history of AWD<sup>(7,9)</sup>, a history of epileptic seizures<sup>(7)</sup>, number of epileptic seizures<sup>(10)</sup>, signs of alcohol withdrawal accompanied by an alcohol concentration of more than 1 gram per liter of body fluid<sup>(7)</sup>, current infectious disease<sup>(7)</sup>, temperature above 38°C during the first 24 hours post-diagnosis<sup>(10)</sup>, a heart rate above 100-120 beats per minute at admission<sup>(7,9)</sup>, systolic blood pressure over 150 mmHg at diagnosis<sup>(10)</sup>. The present study probably did not find those risk factors because of the small sample size.

That patients who had CIWA-Ar scores > 10 on the first day after admission showed a trend to develop AWD, substantiated the previous study that patients with an initial CIWA-Ar score  $\geq 10$  correlated with severity of withdrawal symptoms<sup>(18)</sup>.

Alcohol withdrawal patients have autonomic nervous system dysfunction caused by down-regulation of alpha-2 receptors during the withdrawal period, increasing the risk of uninhibited adrenergic action<sup>(19)</sup>. The finding here that alcohol withdrawal delirium patients with abnormal autonomic nervous system function manifested by higher blood pressure at first admission had a significant longer duration of delirium, reflects previous findings that patients with abnormal autonomic signs of hyperthermia<sup>(10,20)</sup>, a heart rate above 100-120 beats per minute at admission<sup>(7,9)</sup>, and systolic blood pressure over 150 mmHg at diagnosis<sup>(10)</sup> had a higher risk of developing AWD and of increased mortality<sup>(20)</sup>.

The strengths of the present study were: an observational prospective study to find a new incidence of AWD, including all patients with and without risk factors; confirmed diagnosis of delirium by one analyst using DSM-IV and CAM-ICU at the same time everyday; and who followed up all patients daily until any developed AWD, as well as observing patterns and risk factors that prolong the duration of AWD. Furthermore, no investigator was involved in the treatment plan. Primary physicians from two hospitals had their own standard treatment that was not dependent on the research study.

There are, however, some limitations to the present study. First, there was a small sample size. A large sample size should be used in a further study. In addition, other risk factors such as liver function tests, the level of benzodiazepines in plasma, or history of prescribed co-administration of drugs, should be assessed<sup>(21)</sup>.

### Conclusion

In summary, the incidence of AWD in this sample was high despite patients receiving diazepam treatment. Patients who start to develop the initial confusion of AWD should receive a higher dosage of benzodiazepines to prevent and treat AWD acceleration. Although the present study did not find any risk factors for AWD, AWD patients with higher blood pressure at the first admission had a significantly longer duration of delirium. Based on this finding, it would be useful to know whether physicians are aware of these risk factors. Screening tools such as CIWA-Ar and CAM-ICU as well as routine assessment and treatment of autonomic nervous system instability and signs of AWD with adequate doses of benzodiazepines, altogether, may be useful to decrease the morbidity and mortality of AWD.

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### Potential conflicts of interest

None

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## รูปแบบและปัจจัยเสี่ยงของภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์

นักพร บุรพาขจรพงษ์, เบญจลักษณ์ มณีทอง, มานิต ศรีสุรภานนท์

**วัตถุประสงค์:** เพื่อศึกษาถึงอุบัติการณ์ รูปแบบและปัจจัยเสี่ยงของภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ รวมทั้งศึกษาถึงปัจจัยที่ทำให้ภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ซับซ้อนยาวนานขึ้นในผู้ป่วยที่เข้ารับการรักษาแบบผู้ป่วยในเพื่อเลิกแอลกอฮอล์

**วัสดุและวิธีการ:** ผู้นิพนธ์ได้ประเมินผู้ป่วยซึ่งเข้ารับการรักษาที่แผนกจิตเวชของโรงพยาบาลมหาราชนครเชียงใหม่ และศูนย์บำบัดรักษายาเสพติด จังหวัดเชียงใหม่ ตั้งแต่เดือนพฤษภาคม พ.ศ. 2548 ถึง เดือนกันยายน พ.ศ. 2548 โดยไม่นับรวมผู้ป่วยที่มีภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ก่อนรับรักษา ศึกษาอุบัติการณ์การเกิดภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์เปรียบเทียบปัจจัยเสี่ยงและขนาดของยากลุ่มเบนโซไดอาซีปีนระหว่างผู้ป่วยที่เกิดและไม่เกิดภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ รวมทั้งวิเคราะห์ปัจจัยที่ทำให้ภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ซับซ้อนยาวนานขึ้น

**ผลการศึกษา:** มีผู้ป่วยชายเข้าร่วมการศึกษาจำนวน 19 คน ซึ่งผู้ป่วย 10 คน (ร้อยละ 52.6) เกิดภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์แม้จะได้รับการรักษาด้วยยากลุ่มเบนโซไดอาซีปีน ผลการศึกษาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างปัจจัยเสี่ยง เช่น อายุ ประวัติของภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์และประวัติชัก ประวัติของการดื่มแอลกอฮอล์ ความถี่และปริมาณการดื่ม อาการถอนฤทธิ์แอลกอฮอล์เมื่อแรกรับ รวมทั้งขนาดยากลุ่มเบนโซไดอาซีปีน แต่พบว่ากลุ่มผู้ป่วยที่ค่าความดันโลหิตค่าบน (systolic blood pressure) สูงกว่า 120 มิลลิเมตรปรอทขณะแรกรับมีระยะเวลาการเกิดภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ยาวนานกว่ากลุ่มที่มีค่าความดันโลหิตค่าบน (systolic blood pressure) ไม่เกิน 120 มิลลิเมตรปรอท ( $72.0 \pm 53.7$  ชั่วโมงเทียบกับ  $168.0 \pm 24.0$  ชั่วโมงตามลำดับ  $p = 0.038$ )

**สรุป:** จากการศึกษาพบว่าอุบัติการณ์ของภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ค่อนข้างสูงถึงผู้ป่วยจะได้รับการรักษาแล้วก็ตาม แม้ว่าผลการศึกษาไม่พบปัจจัยเสี่ยงของการเกิดภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ แต่พบว่าผู้ที่มีความดันโลหิตค่าบน (systolic blood pressure) สูงกว่า 120 มิลลิเมตรปรอท ขณะแรกรับมีภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์ยาวนานกว่ากลุ่มที่ไม่มีปัญหาดังกล่าว ซึ่งจากผลการศึกษาทำให้แพทย์ผู้ดูแลผู้ป่วยกลุ่มนี้ควรตระหนักถึงภาวะความดันโลหิตสูง ร่วมกับเฝ้าติดตามและรีบให้การรักษาภาวะถอนฤทธิ์แอลกอฮอล์ด้วยยากลุ่มเบนโซไดอาซีปีนในขนาดที่เพียงพอ เพื่อช่วยลดความทุกข์ทรมาน และการเสียชีวิตจากภาวะแพ้จากการถอนฤทธิ์แอลกอฮอล์

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