Withdrawal syndromes

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Background

- Substance and ethanol abuse-related admissions may represent up to 30% of total admissions in some medical or surgical ICU, with usually a poorer long-term outcome
- Abrupt cessation may expose to serious complications including agitation, hallucinations, tachycardia, hypertension or fever, or even death
- Acute management would be improved by the comprehension of the pathophysiology, of the mode of action of pharmacological treatments, and also by well adapted protocols

Alcohol withdrawal

- About 50% of persons with alcohol-use disorders have symptoms of alcohol withdrawal when they reduce or discontinue alcohol consumption
  - 3 to 5% will experience grand mal seizures, delirium, or both
- Withdrawal symptoms usually begin within 8 hours after blood alcohol levels decrease, peak at about 72 hours, and are markedly reduced by day 5 through 7 of abstinence
- The time course and severity of symptoms must be closely monitored using an adapted scale (CIWA-Ar)
  - Scores from 0 to 67
  - <8: mild withdrawal symptoms, few medications required
  - 8-15: moderate withdrawal symptoms, benzodiazepines indicated
  - >15: major risk for seizures and withdrawal delirium

(Schuckit , NEJM, 2014)

Alcohol withdrawal syndrome

Table 1. Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised.*

Components of Scale	Most Severe Manifestations
Nine items scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms)	
Nausea or vomiting	Constant nausea with vomiting
Tremor	Severe tremor, even with arms extended
Paroxysmal sweats	Drenching sweats
Anxiety	Acute panic
Tactile disturbances (itching, numbness, sensation of bugs crawling on or under the skin)	Continuous hallucinations
Auditory disturbances (sensitivity to sound, hearing things that are not there)	Continuous hallucinations
Visual disturbances (sensitivity to brightness and color, seeing things that are not there)	Continuous hallucinations
Headache, sensation of a band around the head	Extremely severe headache
Agitation	Pacing during most of interview with clinician or thrashing about
One item scored on a scale ranging from 0 (no symptoms) to 4 (disoriented with respect to place or person)	
Orientation and clouding of sensorium	

(Schuckit , NEJM, 2014)

Alcohol withdrawal

- Risk factors
  - No prospective study of risk factors leading to identify AWS in the ICU, except for alcohol consumption
  - Prior episodes of AWS or seizures are good predictors of withdrawal in an ICU population
  - Carbohydrate-deficient transferrin elevation is a good indicator of chronic alcohol consumption and has been associated with prolonged ICU stay in trauma patients
  - Blood ethanol at admission is not associated with AWS in the ICU
  - In non-ICU populations, structural brain lesions, infectious medical conditions, genetic predisposition, delays in identification of withdrawal symptoms were considered as risk factors for DT

Alcohol withdrawal delirium

Table 2. DSM-5 Criteria for Withdrawal Delirium (Delirium Tremens).*

Criteria for alcohol withdrawal
Cessation of or reduction in heavy and prolonged use of alcohol
At least two of eight possible symptoms after reduced use of alcohol:
Autonomic hyperactivity
Hand tremor
Insomnia
Nausea or vomiting
Transient hallucinations or illusions
Psychomotor agitation
Anxiety
Generalized tonic–clonic seizures
Criteria for delirium
Decreased attention and awareness
Disturbance in attention, awareness, memory, orientation, language, visuo-spatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day
Disturbances in memory, orientation, language, visuospatial ability, or perception
No evidence of coma or other evolving neurocognitive disorders

(Schuckit , NEJM, 2014)

- Alcohol withdrawal + disturbances of attention and cognition
- True prevalence variable
- Predicted by CIWA-Ar, prior or recent withdrawal delirium or seizures, older age, concomitant medical problems
- Delirium usually begins about 3 days after symptoms of alcohol withdrawal, lasts from 1 to 8 days
- Mortality rate: 1-4%
  - Cardiac arrythmias, seizures, hyperthermia, metabolic disorders

Management of alcohol withdrawal delirium

- 9 prospective controlled trials
  - 5 CT comparing sedative-hypnotics and neuroleptics
  - Sedative-hypnotics are more effective than neuroleptics in reducing mortality
  - No differences between sedative-hypnotics
  - Sedative-hypnotic: shorter duration of AWD

Table 3. Prospective Controlled Trials Reporting Mortality as an Outcome*

Source	Intervention	Route of Administration	Deaths, No./ Patients, Total No.
Friedhoff and Zitrin,[13] 1959	*Chlorpromazine*	IM/PO	0/15
	Paraldehyde	IM/PO	0/16
Thomas and Freedman,[14] 1964	*Promazine*	PO	6/17
	Paraldehyde	PO	1/22†
Chambers and Schultz,[15] 1965	*Promazine* plus chloral hydrate	PO	0/34
	Diazepam	PO	0/35
	Chlordiazepoxide	PO	0/34
Golbert et al,[16] 1967	*Promazine*	IM/PO	2/13
	Paraldehyde and chloral hydrate	IM/PO	0/12
Kaim and Klett,[17] 1972	*Perphenazine*	IM/PO	0/46
	Chlordiazepoxide	IM/PO	0/46
	Pentobarbital	IM/PO	0/41
	Paraldehyde	IM/PO	0/55
Brown et al,[18] 1972	Diazepam	IV	0/7
	Chlordiazepoxide	IV	0/7
Thompson et al,[19] 1975	Diazepam	IV	0/17
	Paraldehyde	Rectal	2/17
Kramp and Rafaelsen,[20] 1978	Diazepam	IM	0/13
	Barbital	PO	0/17
Present meta-analysis	*Neuroleptics* vs sedative-hypnotics		‡

Table 4. Prospective Controlled Trials Reporting Duration of Delirium*

Source	Intervention	Route of Administration	Patients, No.	Duration, h	*P* Value
Friedhoff and Zitrin,[13] 1959	*Chlorpromazine*	IM/PO	15	192	<.05
	Paraldehyde		16	144	
Thomas and Freedman,[14] 1964	*Promazine*	PO	17	96	.04†
	Paraldehyde	PO	22	74	
Golbert et al,[16] 1967	*Promazine*	PO	5	134	..‡
	Paraldehyde/chloral hydrate		11	<24	
Kaim and Klett,[17] 1972	*Perphenazine*	IM/PO	46	77.9	>.20
	Pentobarbital	IM/PO	41	80	
	Paraldehyde	IM/PO	55	78.4	
	Chlordiazepoxide	IM/PO	46	74	
Thompson et al,[19] 1975	Paraldehyde	Rectal	17	57	>.05
	Diazepam	IV	17	55	

(Mayo-Smith et al., Ann Intern Med, 2004)

Alcohol withdrawal

- General AWS treatment strategies
  - Scientific evidence comes mainly from retrospective, randomized, open-label studies
  - A multiple drug approach is usually necessary, with as common drugs benzodiazepines, (clomethiazole), antipsychotics, clonidine, phenobarbital, propofol and dexmedetomidine
  - There is a general consensus for a symptoms-triggered titration as opposed to continuous infusion
  - This strategy aims to reduce the average drug doses needed, ICU stay, length of mechanical ventilation, prevalence of pneumonia, severity and duration of AWS

Alcohol withdrawal

- Benzodiazepines

Benzodiazepines for alcohol withdrawal

1.Laura Amato*,
2.Silvia Minozzi,
3.Simona Vecchi,
4.Marina Davoli (2010)

- 64 studies, 4309 patients
- Comparing BZD *vs* placebo, benzodiazepines performed better for seizures
- Comparing BZD *vs* other drugs, trend in favour of BZD for seizures and delirium control, life-threatening side effects, dropouts and patient's global assessment score. A trend in favour of control group was noted for CIWA-Ar scores
- Comparing BZD among themselves, no statistical difference, trend in favour of chlordiazepoxide
- Comparing BZD + other drug versus other drug, no statistical difference
- Symptoms-triggered regimens performed better

Alcohol withdrawal

- Benzodiazepines: one of the possible dosage regimen
  - Diazepam, 5 mg iv (2,5 mg/min)
  - If the initial dose is not effective, repeat the dose in 5 to 10 min
  - If the second dose of 5 mg is not satisfactory, use 10 mg for the third and fourth doses every 5 to 10 min
  - If not effective, use 20 mg for the fifth and subsequent doses until sedation is achieved
  - Use 5 to 20 mg every hour as needed to maintain light somnolence

Alcohol withdrawal

- Ethanol
  - Experience with ethanol infusion mainly available for prevention of AWS in postoperative and trauma ICU patients
  - Great variation in dose and administration, inconstant ethanol elimination rate in chronic alcoholic patients
  - Only 2 comparative studies, either with BZD or other drugs, with similar rates of prevention
  - Ethanol infusion has numerous side effects, treatment is not recommended for prevention or management of AWS

Alcohol withdrawal

- Antipsychotics
  - Classical (haloperidol) and atypical antipsychotics are used to manage hallucinations and agitation occurring in AWS
  - No study has compared BZD with haloperidool for AWS in ICU
  - Concerns with this drug class: QT prolongation, lowering of seizure threshold, thermoregulation abnormalities
  - May be proposed as adjunctive therapy, after optimization of benzodiazepine use

Alcohol withdrawal

- Clonidine
  - Clonidine is expected to decrease autonomic disturbances in AWS
  - No apparent benefit of the addition of clonidine to BZD for AWS prophylaxis or ICU length of stay
  - Only two randomized controlled studies with clonidine
    - With clonidine also, a symptoms-based strategy is more efficient
    - Comparison flunitrazepam-clonidine vs chlomethiazole-haloperidol and flunitrazepam-haloperidol
      - The flunitrazepam-clonidine group was associated with less pneumonia but more cardiac complications
    - Length of ICU stay not modified
    - Clonidine administration requires titration, ECG monitoring and progressive weaning

Alcohol withdrawal

- Dexmedetomidine
  - Theoretical interest for DEX: inhibition of sympathetic activity, lack of respiratory depression, GABA-independent action
  - Lack of trials comparing DEX to standard agents
  - Case reports and case series in severe AWS in ICU patients after failure of BZD
  - Mainly used as add-on therapy to BZD
  - Expected benefit: reduction of BZD dosage, of AWS severity score and adrenergic symptoms
  - Doses in the median range (0.7 µg/kg/hr) appear efficient, with a rapid evidence of clinical improvement
  - Probably promising as an add-on therapy, fewer cardiac and hemodynamic effects in comparison with clonidine
  - Relatively expensive

Evaluation of Early Dexmedetomidine Addition to the Standard of Care for Severe Alcohol Withdrawal in the ICU: A Retrospective Controlled Cohort Study

Journal of Intensive Care Medicine, 2014

Luke A. VanderWeide, PharmD[1], Charles J. Foster, PharmD[2], Robert MacLaren, PharmD, MPH[3], Tyree H. Kiser, PharmD[3], Douglas N. Fish, PharmD[3], and Scott W. Mueller, PharmD[3]

- Retrospective controlled cohort study, adults admitted to the ICU for > 24 h for AWS
- Patients receiving DEX within 60 h of admission matched to control patients
- Primary outcome: 12-h BZD requirement from the inflection point or DRX initiation
- Secondary outcome: 24-h BZD requirements, symptom control, ICU and hospital LOS, incidence and duration of mechanical ventilation, incidence of bradycardia or hypotension

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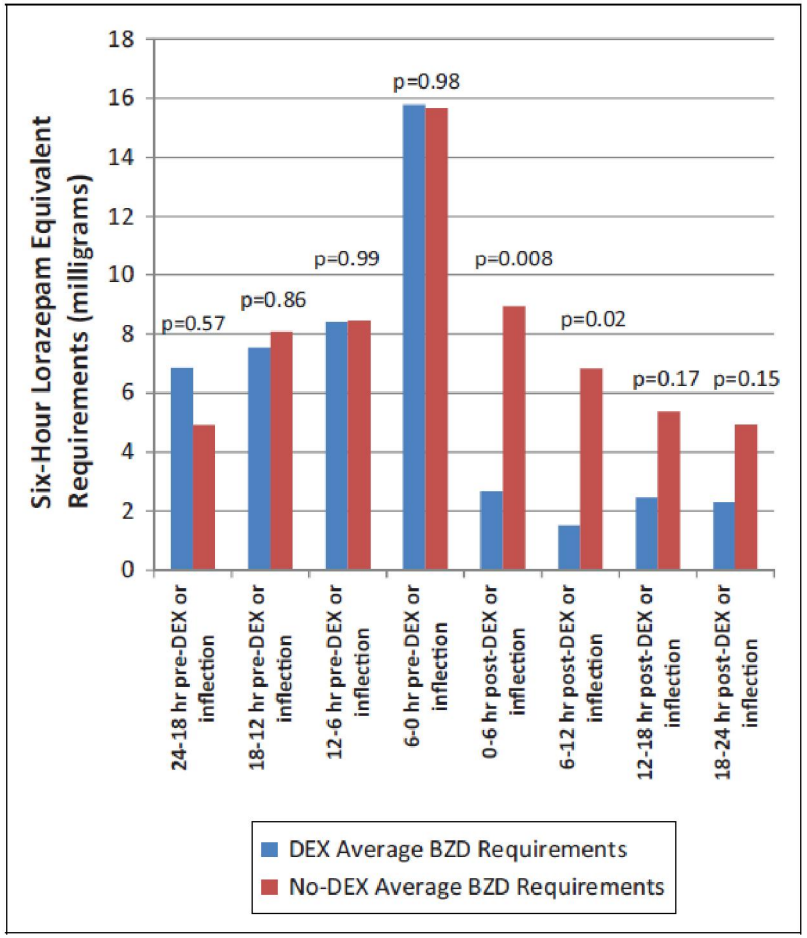

- The mean 12-h change in BZD requirement was lower for the DEX group
- No difference in the secondary outcomes (ICU and hospital LOS, incidence and duration of mechanical ventilation)
- More bradycardia in the DEX group
- Supports the hypothesis that DEX may reduce BZD requirements

Alcohol withdrawal

- Propofol

Use of Propofol-Containing Versus Benzodiazepine Regimens for Alcohol Withdrawal Requiring Mechanical Ventilation

Annals of Pharmacotherapy
2014, Vol. 48(4) 456–461

Rose Sohraby, PharmD, BCPS[1,2,3,4,5],
Rebecca L. Attridge, PharmD, MSc, BCPS[1,3,4], and
Darrel W. Hughes, PharmD, BCPS[1,2,3]

- Problem of definition of benzodiazepines refractory AWS
- Few data comparing propofol-containing *versus* benzodiazepines regimens in patients with AWS requiring mechanical ventilation
- No differences regarding duration of AWS, length of ICU or mechanical ventilation
- Potential advantages of propofol: easy titration, few residual sedation

Alcohol withdrawal

- Baclofen

Baclofen for alcohol withdrawal

1.Jia Liu*,

2.Lu-Ning Wang (2015)

  - 113 references from all electronic databases searched excluding duplicates, full papers of 10 studies assessed for eligibility, two RCTs with 81 participants were eligible
  - Results: regarding the efficacy, one study suggested that both baclofen and diazepam significantly decreased the Clinical Institute Withdrawal Assessment of Alcohol Scale Revised (CIWA-Ar) score, without any significant difference between the two interventions. The other study showed no significant difference in CIWA-Ar score between baclofen and placebo but a significantly decreased dependence on high-dose benzodiazepines with baclofen compared to placebo.
  - Meanwhile, only one study reported the safety outcomes and there were no side effects in either the baclofen or diazepam groups.
  - Abrupt cessation can lead to severe and life-threatening withdrawal characterized by altered mental status, autonomic dysreflexia, rigidity, and seizures. This symptomatic presentation is similar to alcohol withdrawal

Benzodiazepine withdrawal

- The incidence of withdrawal symptoms may vary from 15 to 44% in the patients chronically treated by BZD
- Risks of withdrawal are increasing after 3 months of treatment
- Symptoms usually include: anxiety, insomnia, fever, tremor, nausea, tinnitus, myalgias, seizures, vomiting, diaphoresis…
- The onset of symptoms may be as short as 1 day for the long-acting BZD
- Symptoms may last for 6 weeks
- The re-introduction of a long-acting BZD appears logical, with a gradual taper over 6-8 weeks
- Phenobarbital has been also found useful in some difficult cases

SSRI withdrawal

- Should SSRI be added to the list of drugs inducing discontinuation or withdrawal syndrome? Association of somatic and psychological symptoms resulting in patient's distress
- Systematic literature review: 15 RCT, 4 open trials, 4 retrospective studies, 38 case reports
  - The prevalence of withdrawal syndrome is difficult to estimate
  - Withdrawal syndrome may occur with any type of SSRI, but is more frequent with paroxetine
  - Withdrawal syndrome occurs typically within a few days and lasts a few weeks
  - Clinical manifestations encompass both physical and psychological symptoms
  - Gradual tapering does not prevent the onset of withdrawal phenomena
  - Pathophysiology: decreased serotonin availability? Stress response with increased hippocampal NMDA receptors density?
  - No evidence that a reintroduction of a long-acting SSRI is helpful
  - Further research is needed with an appropriate methodology

(Fava et al., Psychother Psychosom, 2015)

Cocaine withdrawal

- Cocaine withdrawal is characterized by 3 consecutive phases
  1. « Cocaine crash » phase (fatigue, insomnia, depression) lasting for 1-2 days
  2. Withdrawal phase (dysphoria, paranoia, agitation, inability to sleep)
  3. Extinction phase
- Craving +++ at any time
- Symptoms would result from depletion of biogenic amine stores
- Clinical management is mainly based on BZD administration

Cannabis withdrawal syndrome

- Cannabis is the most common illicit drug used in the world, with an estimated 160 million current users worldwide
- Approximately 10% of cannabis users will become dependent
- Odds of developping dependence are one in two for daily users
- A high proportion of frequent cannabis users report experiencing a withdrawal syndrome after stopping use, ranging from 15.6 to 40.9%
- Heavy daily users may experience withdrawal symptoms of insomnia, diaphoresis, dysphoria, irritability, tremor and nausea
- Symptoms peak at 48 h of abstinence and persist for 96 h
- There is no recognized withdrawal regimen for THC ingestion, most of the users resume cannabis consumption

Controversies in cannabis withdrawal syndrome

- Compared with other illicit substances the definition of a cannabis withdrawal syndrome (CWS) had remained controversial
  - Few evidence available of increasing tolerance associated with cannabis use
- Recent prospective study assessing the course of CWS symptoms among patients dependent on cannabis who were seeking detoxification.
- This study seems to support evidence of a clinically relevant CWS that the authors qualify as only expected in a subgroup of cannabis-dependent patients
- CWS specified symptoms are believed to occur following a 24-hour period of abstinence, peaking at day 3 following abstinence and lasting 1-2 weeks
- Risk factors that seemed to predict which subgroup patients (mild or moderate-strong CWS) could be classified by included recent cannabis intake and last amount of cannabis consumed prior to hospitalization, with patients reporting recent and more cannabis consumption before hospitalization as more likely to report symptoms of CWS

Controversies in cannabis withdrawal syndrome

- CONTRA
  - No clear scientific evidence that cannabis induces a physical dependence
  - Symptoms of cannabis withdrawal are poorly specific and subjective, they do not prove by themselves the reality of physical dependence
  - Numerous bias in the clinical studies on cannabis withdrawal
    - Great variability in the form (oral or smoking) and dose of cannabis, great variability in THC concentrations when available
    - Role of environment (lab versus real life conditions), experimental conditions
    - Role of other susbtances (alcohol, nicotine)
    - Role of underlying psychiatric disorders

Controversies in cannabis withdrawal syndrome

- PRO
  - Epidemiological evidence that heavy daily users have major difficulties to stop or develop symptoms that can only be controled by resumption of the drug
  - Withdrawal symptoms develop in patients who are or not seeking for treatment, who have no underlying psychiatric disorders, who are not abusing of other substances…
  - Experimental models suggest also that cannabis cessation is associated with physical symptoms (loss of appetite, sleep disorders,…)
  - There is a pharmacological relationship between the intensity of cannabis use and the severity of withdrawal symptoms
  - Expiremental models influencing the endogenous cannabinoid system

DSM V criteria for cannabis withdrawal

- Cessation of cannabis use that has been heavy and prolonged (ie, usually daily or almost daily use over a period of at least a few months).
- Three or more of the following signs and symptoms develop within approximately 1 week after cessation of heavy, prolonged use:
  - Irritability, anger or aggression
  - Nervousness or anxiety
  - Sleep difficulty (ie, insomnia, disturbing dreams)
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
  - At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Characteristics of cannabis withdrawal symptoms

Characteristics of cannabis withdrawal symptoms reported by 384 adult, non-treatment-seeking cannabis smokers.

Withdrawal symptom[e]	% (*n*) subjects reporting	Onset after quitting (days) (mean [SD])	Peak intensity[f] (mean [median])
Craving for cannabis (1)	59.4% (228)	4.4 (0.9)	4.4 (5.0)
Insomnia[a] (1)(3)	48.7% (187)	2.7 (5.0)	3.8 (4.0)
Strange and/or vivid dreams (1)	10.4% (40)	3.7 (5.5)	3.7 (4.0)
Sleep difficulties[b] (2)	50.5% (194)	2.6 (4.9)	3.8 (4.0)
Increased appetite	20.8% (80)	3.3 (6.1)	4.0 (4.0)
Decreased appetite	17.4% (67)	4.0 (7.3)	3.6 (4.0)
Change in appetite[c] (1)	36.4% (140)	3.7 (5.9)	3.9 (4.0)
Weight loss	7.3% (28)	10.3 (10.2)	2.9 (3.0)
Weight loss and/or decreased appetite (2)(3)	20.8% (80)	4.9 (8.1)	3.5 (4.0)
Feeling sad, depressed (1)(2)(3)	34.4% (132)	4.0 (6.7)	3.7 (4.0)
Feeling irritable, "jumpy" (1)(2)	29.4% (113)	3.3 (6.1)	3.7 (4.0)
Feeling anxious, "nervous" (1)(2)(3)	38.5% (148)	3.4 (6.5)	3.6 (3.0)
Feeling restless (1)(2)(3)	21.9% (84)	2.8 (4.4)	3.7 (4.0)
Feeling angry	28.9% (111)	3.1 (5.7)	3.9 (4.0)
Feeling aggressive	20.1% (77)	3.6 (5.6)	3.8 (4.0)
Feeling angry and/or aggressive (1)(2)	33.9% (130)	2.8 (5.4)	3.9 (4.0)
Feeling angry and/or aggressive and/or irritable (3)	45.6% (175)	3.0 (5.5)	3.9 (4.0)
Physical discomfort	8.9% (34)	4.4 (8.4)	3.9 (4.0)
Physical symptom[d] (3)	25.3% (97)	3.1 (5.0)	3.6 (4.0)
Tremor/shakiness (2)	4.9% (19)	1.6 (1.4)	3.2 (3.0)
Nausea and/or vomiting (1)	5.2% (22)	3.2 (6.4)	3.4 (3.0)
Diarrhea and/or stomach pains and/or upset stomach (1)	14.1% (54)	2.5 (4.4)	3.3 (3.0)
Stomach pains (2)	8.3% (32)	1.9 (2.1)	3.4 (3.5)
Chills (2)	3.4% (13)	2.2 (3.9)	3.0 (3.0)
Headaches (1)	16.9% (65)	3.7 (5.9)	3.4 (3.0)
Sweating (2)	5.5% (21)	2.2 (2.2)	3.8 (4.0)

Quantifying the Clinical Significance of Cannabis Withdrawal

David J. Allsop[1]*, Jan Copeland[1], Melissa M. Norberg[1], Shanlin Fu[2], Anna Molnar[2], John Lewis[2], Alan J. Budney[3]

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- How to quantify functional impairment to daily activities from cannabis withdrawal?
- A volunteer sample of 49 non-treatment seeking cannabis users
- One-week base line phase followed by two weeks of monitored abstinence
- 19 items covering various symptoms, with an intensity of 0-10; also the negative impact of withdrawal symptoms on daily activity, with an intensity of 0-10

Quantifying the Clinical Significance of Cannabis Withdrawal

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Table 1. The cannabis withdrawal scale.

Not at all						Moderately					Extremely		Negative Impact on daily activity (0–10)
1	The only thing I could think about was smoking some cannabis	0	1	2	3	4	5	6	7	8	9	10	
2	I had a headache	0	1	2	3	4	5	6	7	8	9	10	
3	I had no appetite	0	1	2	3	4	5	6	7	8	9	10	
4	I felt nauseous (like vomiting)	0	1	2	3	4	5	6	7	8	9	10	
5	I felt nervous	0	1	2	3	4	5	6	7	8	9	10	
6	I had some angry outbursts	0	1	2	3	4	5	6	7	8	9	10	
7	I had mood swings	0	1	2	3	4	5	6	7	8	9	10	
8	I felt depressed	0	1	2	3	4	5	6	7	8	9	10	
9	I was easily irritated	0	1	2	3	4	5	6	7	8	9	10	
10	I had been imagining being stoned	0	1	2	3	4	5	6	7	8	9	10	
11	I felt restless	0	1	2	3	4	5	6	7	8	9	10	
12	I woke up early	0	1	2	3	4	5	6	7	8	9	10	
13	I had a stomach ache	0	1	2	3	4	5	6	7	8	9	10	
14	I had nightmares and/or strange dreams	0	1	2	3	4	5	6	7	8	9	10	
15	Life seemed like an uphill struggle	0	1	2	3	4	5	6	7	8	9	10	
16	I woke up sweating at night	0	1	2	3	4	5	6	7	8	9	10	
17	I had trouble getting to sleep at night	0	1	2	3	4	5	6	7	8	9	10	
18	I felt physically tense	0	1	2	3	4	5	6	7	8	9	10	
19	I had hot flashes	0	1	2	3	4	5	6	7	8	9	10	

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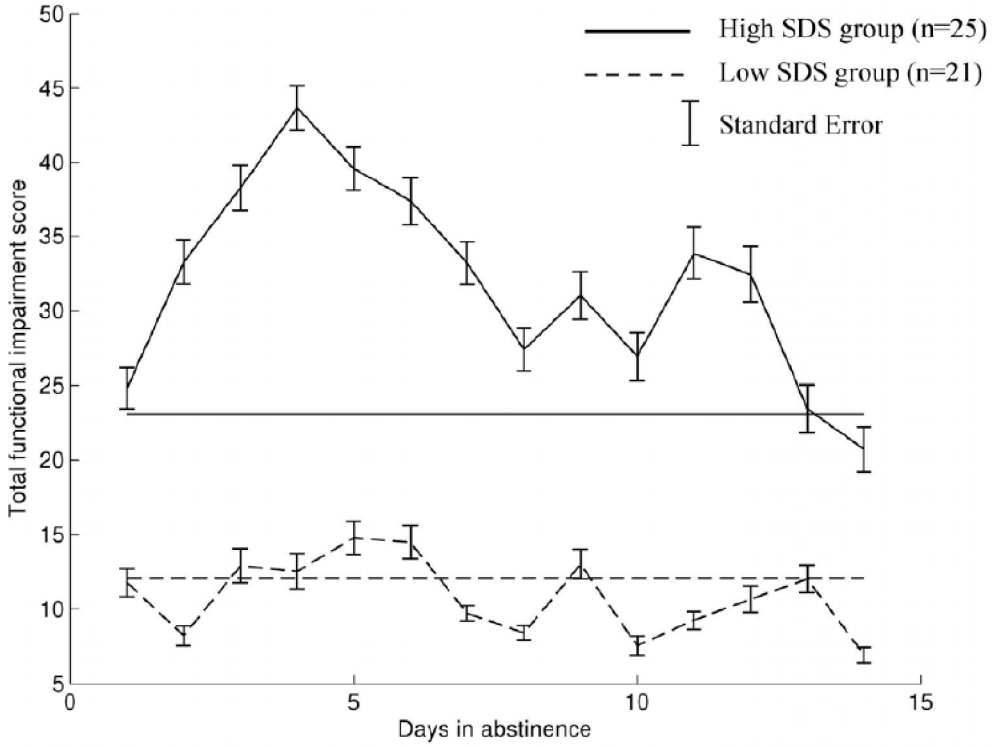

- Higher levels of dependence on cannabis were associated with higher levels of functional impairment from cannabis withdrawal
- The strongest predictor of functional impairment to normal daily activities from cannabis withdrawal was the severity of the cannabis withdrawal symptoms
- Higher levels of functional impairment during the abstinence attempt predicted higher levels of cannabis use at one month follow-up

Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal

A Randomized Clinical Trial

David J. Allsop, PhD; Jan Copeland, PhD; Nicholas Lintzeris, PhD; Adrian J. Dunlop, PhD;
Mark Montebello, FAChAM; Craig Sadler, FAChAM; Gonzalo R. Rivas, BNurs; Rohan M. Holland, BNurs;
Peter Muhleisen, BPharm, MPSA; Melissa M. Norberg, PhD; Jessica Booth, BSc (Hons); Iain S. McGregor, PhD

- Background: no approved therapy for managing cannabis withdrawal
  - A range of medications (bupropion, lithium, lofexidine) has shown limited benefits
- Objective: to evaluate the safety and efficacy of nabiximols in treating cannabis withdrawal
- Material and methods: double-blind RCT with a 28-day follow-up, including 51 cannabis-dependent treatment seekers
- Intervention: 6-day regimen of nabiximols (max daily dose, 86,4 mg of Δ9-THC and 80 mg of cannabidiol) or placebo, psychosocial interventions during 9 days
- Outcomes: severity of cannabis withdrawal and cravings, retention in withdrawal treatment, adverse events. Secondary outcome: postwithdrawal cannabis use

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- Nabiximols treatment significantly reduced the overall severity of cannabis withdrawal: irritability, depression, cannabis cravings
- More limited effect on sleep disturbance, anxiety, appetite loss, physical symptoms and restlessness
- Nabiximols treated patients remained in treatment longer during medication use
- No serious adverse effects
- But at follow-up, no difference between nabiximols and placebo for self-reported cannabis use, cannabis-related problems or cannabis dependence
- Limitations of an inpatient setting study

Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal
A Randomized Clinical Trial

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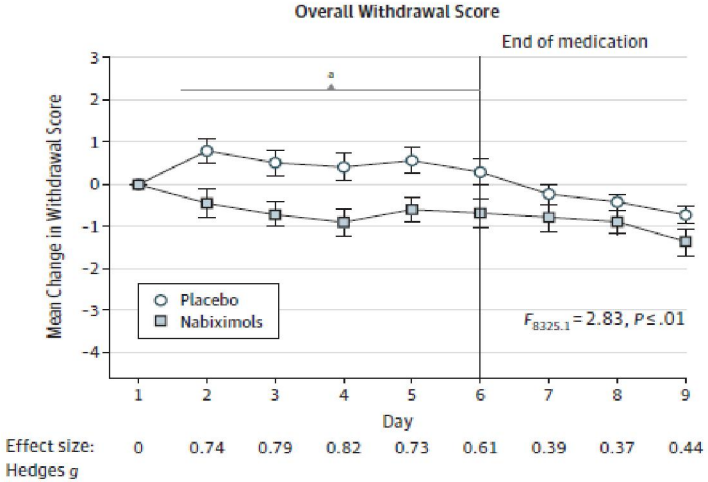

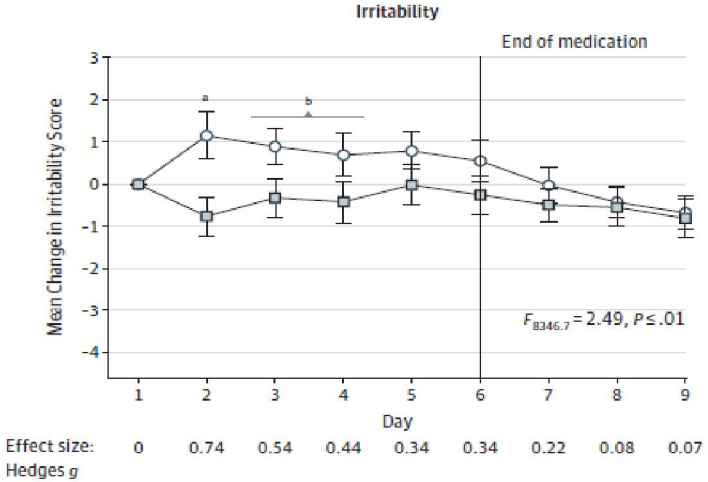

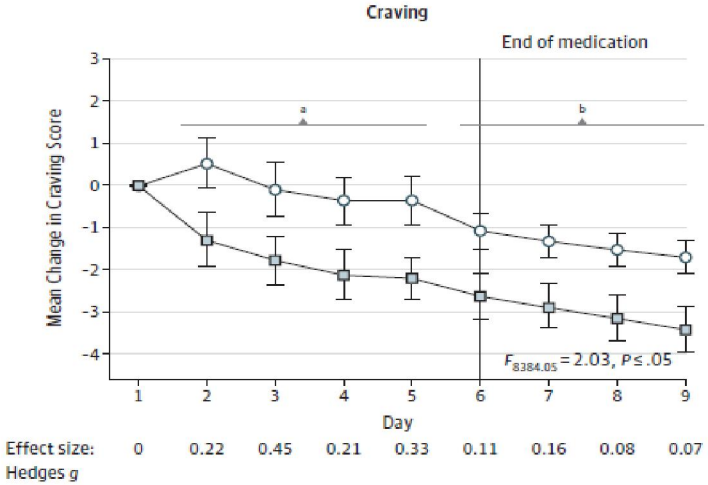

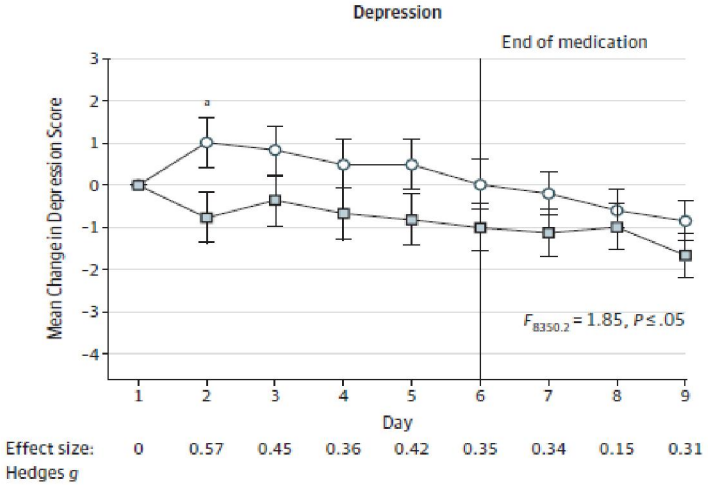

Synthetic cannabinoid withdrawal: A new demand on detoxification services

Drug and Alcohol Review (March 2015), 34, 147–153

VICKI MACFARLANE[1] & GRANT CHRISTIE[2]

[1]*Medical Detoxifications Services, Community Alcohol and Drug Services, Waitemata District Health Board, Auckland, New Zealand, and* [2]*Youth Services, Community Alcohol and Drug Services, Waitemata District Health Board, Auckland, New Zealand*

- Knowledge about the short- or long-term effects of synthetic cannabinoids is progressing
- There are a limited number of case reports of intoxication or withdrawal/depence symptoms
- Pharmacological studies suggest that psychotropic and adverse effects of synthetic cannabinoids are similar to, or even stronger, than those of natural cannabis
- Prior to May 2014, more than 300 types of synthetic cannabinoids were available from retail stores in New Zealand
- A increasing number of patients is presenting to « walk-in » clinics in order to obtain support to stop synthetic cannabinoids

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- Retrospective analysis on 47 patients (self-referred or addressed) (6 times more than the patients presenting for natural cannabis)
- Heavy users: mean daily use 4.6 g, wide range of different types/brands of synthetic cannabinoids
- Development of withdrawal symptoms: anxiety, mood swings, nausea, loss of appetite
- Symptoms occur within 1-2 h of last use
- In-patients treatment
  - Mean duration of admission: 8 days
  - Medications used: diazepam on an as-required basis, quetiapine if diazepam ineffective
  - Mean duration of diazepam treatment 4 days, mean duration of quetiapine treatment 8 days
  - On the average 5 to 25 mg diazepam daily, 25 to 475 mg quetiapine
  - Quetiapine was found more effective than diazepam for the treatment of agitation, anxiety and irritability

Opioid withdrawal

- α2-adrenergic agonists

Alpha$_2$-adrenergic agonists for the management of opioid withdrawal

1.Linda Gowing[1,*],
2.Michael F Farrell[2],
3.Robert Ali[1],
4.Jason M White[3] (2014)

- Effectiveness of interventions involving the use of α2-adrenergic agonists (clonidine, lofexidine) compared with placebo, reducing doses of methadone, symptomatic medications or with comparison of different α2-adrenergic agonists for the management of the acute phase of opioid withdrawal
- Outcomes: intensity of signs and symptoms and overall withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects and completion of treatment
- 25 randomised controlled trials, 1668 patients
  - 5 with α2-adrenergic agonist versus placebo, in 12 with a regimen based on reducing doses of methadone, in 4 with symptomatic medications, and 5 comparisons with different α2-adrenergic agonists

Opioid withdrawal

- α2-adrenergic agonists

Alpha$_2$-adrenergic agonists for the management of opioid withdrawal

1.Linda Gowing[1,*],
2.Michael F Farrell[2],
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4.Jason M White[3] (2014)

  - Results:
  - α2-adrenergic agonists more effective than placebo for the intensity of withdrawal symptoms and completion of R/
  - α2-adrenergic agonists somewhat less effective than reducing doses of methadone in ameliorating withdrawal symptoms but NS
  - Signs and symptoms of withdrawal resolved earlier with α2-adrenergic agonists
  - Duration of treatment was significantly longer with methadone
  - Hypotensive effects more frequent with α2-adrenergic agonists
  - Insufficient data to compare α2-adrenergic agonists (dexmedetomidine not included in the review)
  - No evidence of superiority of α2-adrenergic agonists

Opioid withdrawal

- Methadone

Methadone at tapered doses for the management of opioid withdrawal

Laura Amato[1,*], Marina Davoli[1], Silvia Minozzi[1], Eliana Ferroni[2], Robert Ali[3], Marica Ferri[4] (2013)

  - Effectiveness of tapered methadone with other detoxification treatments and placebo in managing opioid withdrawal
  - 23 trials invloving 2467 people
  - Methadone versus any other pharmacological treatment or single comparisons (vs adrenergic agonists, other opioid agonists,…)
    - No clinical difference in terms of completion of treatment, abstinence at follow-up, degree of discomfort of withdrawal symptoms and adverse effects
    - Methadone superior to placebo (severity of withdrawal, drop-outs)
  - Limitations: wide variability in the detoxification programs, significant relapse of heroin use

GHB/GBL/1,4-BD withdrawal

- GHB withdrawal established, may be prolonged and severe
- Symptoms (anxiety, tremor, confusion, delirium, hallucinations, but also dyasautonomia) within 1-6 h and lasting for 3-15 days; similar for GHB or GBL withdrawal
- Treatment based on high-doses benzodiazepines regimen, but resistance is possible (no action on $GABA_B$), and admission to the ICU may be required
  - Alternative treatments: pentobarbital, propofol ,clonidine, gabapentine, neuroleptics, or pharmaceutical GHB (high rate of detoxification, but high incidence of relapse)
  - Recent interest for baclofen as a $GABA_B$ agonist, but with the issue of a possible baclofen withdrawal syndrome

Nicotine withdrawal

- About 20-46% ICU patients are estimated to be smokers
- Nicotine withdrawal has been identified as one of the risk factors for agitation and delirium
- A prospective observational cohort study that compared smokers with nonsmokers demonstrated that current smoking history is associated with an increased frequency of agitation and related adverse events, removal of tubes and catheters, need for supplemental doses of sedatives, analgesics and neurolpetics, and requirement for physical restraints (Lucidarme et al., Crit Care Med, 2010)
- However, nicotine withdrawal in ICU is not well characterized

Nicotine withdrawal

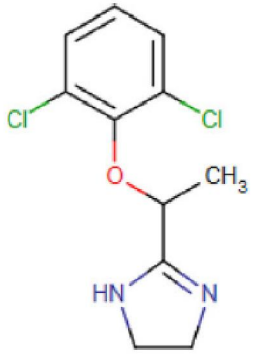
- Diagnostic criteria for nicotine withdrawal according DSM-IV
  - Anger, irritabilility, frustration, anxiety, dysphoria, concentration difficulties, impatience, sleep fragmentation, insomnia, restlessness, weight gain, and bradycardia
  - Symptoms were mostly described for outpatients
  - Withdrawal syndrome starts after 1-2 days of abstinence, with a peak within the first week, and resolution within the next 2-4 weeks
- Management of nicotine withdrawal
  - Outpatients: nicotine replacement therapy (NRT) is considered as safe and effective
  - ICU patients: limited data for safety in ICU patients, some retrospective studies even suggested that mortality was higher in patients with NRT
  - NRT often prescribed as an alternative or additional pharmacologic intervention for agitation or delirium when anxiolytics have failed
  - Role of α2-adrenergic receptor agonists in attenuating stress-induced nicotine craving?

Conclusion

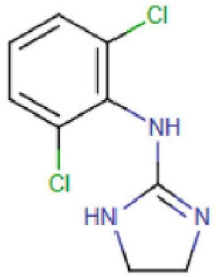
- Alcohol withdrawal:
  - no prophylaxis can be unequivocally recommended
  - a symptoms-based strategy is superior to continous infusion of drugs
  - benzodiazepines as first-line treatment
  - propofol and dexmedetomidine to be further investigated
- Benzodiazepines and cocaine withdrawal:
  - importance of symptomatic treatment
- SSRI withdrawal:
  - gradual tapering?
- Cannabis and synthetic cannabinoids withdrawal:
  - withdrawal syndrome still controversial, and also pharmacological treatment
- Opioid withdrawal:
  - large variability of detoxification programs
  - methadone treatment: long duration, risks for naive population, risks of dosage errors, buprenorphine safer in comparison with previous experience with methadone in the same population
- GHB/GBL withdrawal:
  - interest for baclofen?
- Nicotine withdrawal:
  - no demonstrable evidence that NRT could be beneficial for ICU patients

Adjunctive therapies for alcohol withdrawal

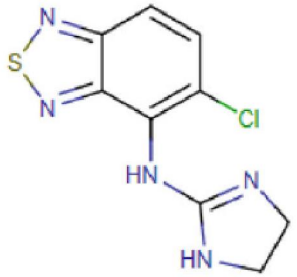
Place of α2-adrenoceptor agonists



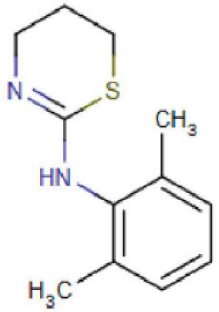
Lofexidine



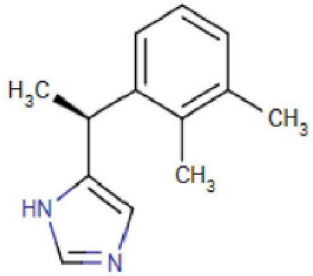
Clonidine



Tizanidine



Xylazine



Dexmedetomidine

Clonidine for alcohol withdrawal syndrome

- There is a consensus to affirm that clonidine has an important potential adjunctive role in AWS

Dexmedetomidine for alcohol withdrawal syndrome