STOMACH

Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse

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Background and aims: To explore the association between chronic cannabis abuse and a cyclical vomiting illness that presented in a series of cases in South Australia.
Methods: Nineteen patients were identified with chronic cannabis abuse and a cyclical vomiting illness. For legal and ethical reasons, all patients were counselled to cease all cannabis abuse. Follow up was provided with serial urine drug screen analysis and regular clinical consultation to chart the clinical course. Of the 19 patients, five refused consent and were lost to follow up and five were excluded on the basis of confounders. The remaining nine cases are presented here and compared with a published case of psychogenic vomiting.
Results: In all cases, including the published case, chronic cannabis abuse predated the onset of the cyclical vomiting illness. Cessation of cannabis abuse led to cessation of the cyclical vomiting illness in seven cases. Three cases, including the published case, did not abstain and continued to have recurrent episodes of vomiting. Three cases rechallenged themselves after a period of abstinence and suffered a return to illness. Two of these cases abstained again, and became and remain well. The third case did not and remains ill. A novel finding was that nine of the 10 patients, including the previously published case, displayed an abnormal washing behaviour during episodes of active illness.
Conclusions: We conclude that chronic cannabis abuse was the cause of the cyclical vomiting illness in all cases, including the previously described case of psychogenic vomiting.

South Australia has had more liberal laws than much of the Western World for some years now regarding the possession of small quantities of cannabis for domestic consumption.[1 2] In the Adelaide Hills area, it has become apparent that what was previously described as "psychogenic vomiting"[3] is often, in fact, cannabis related illness. This disorder, occurring in susceptible individuals, is characterised by: a history of several years of cannabis abuse, predating the onset of the vomiting illness; the hyperemesis follows a cyclical pattern every few weeks or months, often for many years, against a background of regular cannabis abuse; cessation of cannabis leads to cessation of the cyclical vomiting illness, as confirmed by a negative urine drug screen for cannabinoids; a return to regular cannabis use heralds a return of the hyperemesis many weeks or months later; and the patient will "compulsively bathe" (that is, will take multiple hot showers or baths only during the active phase of the illness).

METHODS

Nineteen patients were identified following an original clinical observation by Allen linking chronic cannabis abuse to a cyclical vomiting illness in several cases in South Australia in 2001. Patients were either referred by doctors (12 cases), self referred (two cases), or identified on the ward by the nursing staff (five cases) during acute admission for profuse vomiting. Of these 19 patients, five refused consent and were lost to follow up and 14 fully consented for publication and presentation. Each patient was allotted a letter of the alphabet to preserve anonymity. Patients were followed up with serial urine drug screens and regular clinical consultations to chart their clinical course.

Inpatients were observed with particular reference to autonomic changes in body temperature (measured tympanically), blood pressure, heart rate, fluid intake, skin flushing, and perspiration. However, patient anxiety, compounded by the severity of the hyperemesis, made formal autonomic testing impossible.

All reasonable efforts were made to exclude confounding causes for their cyclical vomiting given the resources at hand. As a result, five patients were excluded from the study for the following reasons:

- Polydrug use (patients O and C).
- Porphyria cutanea tarda (patient Z).
- Acute pancreatitis (patient B).
- Schizophrenia (patient T).

The remaining nine cases are presented in tables 1–4. They were compared with a case of psychogenic vomiting described in 1996 by de Moore and colleagues.[4]

In their article, de Moore and colleagues[4] described in detail a man (Mr G), who had smoked marijuana as a teenager, developed a cyclical vomiting syndrome in his twenties, and was noted to have multiple showers on the ward. Marijuana was not proposed as a cause of his illness.

RESULTS

The results of the study are presented in tables 1–4. The findings were as follows:

(a) there was a delay of several years in the onset of the vomiting illness in all cases against a background of ongoing cannabis abuse. In all cases, chronic marijuana abuse predated the cyclical vomiting syndrome;
(b) cessation of cannabis abuse led to cessation of the cyclical vomiting illness in seven patients (X, Y, A, Q, J, K, and L);
(c) three patients (R, E, and G) did not abstain and continued to have episodes of vomiting;

Table 1 Characteristics of the first five study subjects

	Mr Y	Mrs X	Mr A	Mr Q	Mr R
Cannabis use age of onset (y)	19	17	16	17	12
Cyclical vomiting (y)	22	20	22	34	17
Illness duration (y)	15mths	9	12	3	4
Cannabis cessation	Well for 9mths//2y	Well for 4y//2y	Well for 18mths	Well for 18mths	Did not cease
Cannabis resumption	Vomiting at 8 weeks	Vomiting at 3mths	Nil	NIL	Ongoing illness
Compulsive bathing	Multiple hot showers	Multiple hot baths	Multiple hot baths	Multiple hot showers	Multiple hot showers
Prodromal illness	Yes (6mths)	No	Yes (1 y)	No	No
Cannabis dose (daily dose)	Heavy (5–10 cones)	Light (1–5 cones)	Heavy (5–10 cones)	Heavy (5–10 cones)	Heavy (5–10 cones)
Noted dose response (increased cannabis use)	Yes (increased for back pain)	–	–	Yes (increased for anxiety)	–
Hospital admissions	Multiple	Multiple	Multiple	Multiple	Multiple
IVI fluids	Required	Required	Required	Required	Required
Cyclical presentation (months)	1–2	2–3	2–3	1–2	3–4
Pyrexia (noted in ward notes)	Not noted	Noted	Not noted	Not noted	Noted
Thirst	+++	+++	+++	+++	+++
Weight loss (kg) (during illness)	10	10	10	Nil	10
Weight gain (kg) (on cessation)	10 (at 3mths)	10 (at 3mths)	10 (at 6mths)	Nil	Nil
Other illicit drugs used	None	None	None	None	None
Alcohol abuse	None	None	None	None	Moderate
Medications	PPI	PPI	PPI	PPI	PPI
PmHx hyperemesis gravidarum	–	Severe	–	–	–
Psychiatric Dx	None	None	None	None	None

PPI, proton pump inhibitors; PmHx, past medical history.

(d) three patients (X, Y, and K) rechallenged themselves after a period of abstinence and all suffered a return to illness and hospital admission. Two of these patients (X and Y) subsequently abstained again from cannabis and got better and remain well. Miss K, however, has not, and remains ill.

Collateral features included a prodromal illness in four cases (Y, A, L, and G) of episodic early morning nausea or vomiting on one or more days per week. This predated the cyclical hyperemesis by months or years. The cyclical hyperemesis occurred in all cases. The severity of illness was reflected by the frequency of hospital admissions and necessity for intravenous fluids.

A novel finding was a ''compulsive bathing'' or washing behaviour noted in nine of 10 patients (X, Y, A, Q, R, J, K, E, and G). These patients would have multiple hot showers or baths on the ward. This ritual became the patients primary preoccupation, with them often waking at night to perform it.

A number of cases had marked weight loss in the range of 5–10 kg during their illness (Y, X, A, R, K, E, and G), with marked weight gain of approximately 5 kg following 3–6 months of abstinence (Y, X, A, J, K). Neither anorexia nervosa nor bulimia was a noted feature of the disease process. None of the patients exhibited abnormal fear of weight gain or body image distortion.

Several patients displayed a dose related response to increased cannabis use (Y, Q, J, E, G) where cannabis was employed as either an anxiolytic or analgesic. Low grade pyrexia was noted after bathing in two cases (X and R), with marked thirst and polydipsia in five cases (Y, X, A, Q, and R). An occasional neutrophilia was noted in six cases (Y, X, A, R, K, and G). A positive cannabinoid urine drug screen was present in all cases (detected at levels >50 μ/l). Significant oesophagitis was diagnosed in five of the cases (modified

Table 2 Characteristics of the remaining four study subjects and the case of psychogenic vomiting described in 1996 by de Moore and colleagues (Mr G*)[4]

	Mr J	Miss K	Mr L	Mr E	Mr G*
Cannabis use age of onset (y)	17	12	14	18	14
Cyclical vomiting (y)	44	14	17	32	20
Illness duration (y)	4	3	6mths	6	3
Cannabis cessation	Well for 2y	Well for 1y	Well for 2y	Did not cease	Did not cease
Cannabis resumption	Nil	Vomiting at 2mths	Nil	Ongoing illness	Ongoing illness
Compulsive bathing	Multiple hot showers	Multiple hot baths	Absent	Multiple hot showers	Multiple hot showers
Prodromal illness	No	No	Yes (6mths)	No	Yes
Cannabis dose (daily dose)	Heavy (5–10 cones)	Moderate (3–4 cones)	Heavy (5–10 cones)	Heavy (5–10 cones)	Heavy (5–10 cones)
Noted dose response (increased cannabis use)	Yes (increased for back pain)	–	–	Yes (increased for anxiety)	Yes (increased for anxiety)
Hospital admissions	Nil	Multiple	Nil	Multiple	Multiple
IVI fluids	Nil	Required	Nil	Required	Required
Cyclical presentation (months)	4–6	2–3	3	3–4	6–12
Pyrexia (noted in ward notes)	–	Not noted	–	Not noted	–
Thirst	++	++	+	++	–
Weight loss (kg) (during illness)	Nil	10	Nil	10	7
Weight gain (kg) (on cessation)	10 (at 6mths)	10 (at 3mths)	Nil	–	–
Other illicit drugs used	None	None	None	None	None
Alcohol abuse	None	None	None	None	None
Medications	Nil	PPI	Nil	PPI	–
PmHx hyperemesis gravidarum	–	Severe	–	–	–
Psychiatric Dx	None	None	None	None	?Anxiety

PPI, proton pump inhibitors; PmHx, past medical history.

Savary-Miller criteria: Y (grade 4), A (grade 2), R (grade 2), K (grade 2), and G). Y was the only patient to have gastric emptying studies performed acutely, displaying severely delayed gastric emptying for solids and liquids. X and A had normal studies but these were performed between episodes of illness. There was a past medical history of severe hyperemesis gravidarum (requiring hospital admission and IVI fluids) for both of the women in the study (X, K).

DISCUSSION

We found that vomiting may present in a prodromal form initially or may proceed directly to the hyperemetic stage. The phenomenon of compulsive bathing behaviour is discussed, as is a differential diagnosis, clinical management, and possible pathophysiological pathways.

Prodromal illness

Chronic cannabis abuse predated the onset of the prodromal illness. For some months or years, prior to the onset of cyclical hyperemesis, several patients (Y, A, L, and G) described the onset of early morning nausea and vomiting on one or more days a week. These patients reported nausea at the sight or smell of food and ''fear of vomiting''. However, unlike patients with anorexia nervosa or bulimia, they maintained normal eating patterns. Appetite was normal. Weight loss was a common feature at this stage in the presentation. Compulsive bathing was minimal or absent.

Hyperemetic presentation

This component of the illness was relatively stereotyped. The patients would start to profusely vomit, often without warning. Nausea, sweating, colicky abdominal pain, and polydipsia often accompanied these events. Patients would take multiple hot baths or showers in an attempt to quell the hyperemesis. Most attempted to cope at home unless they exhausted their hot water supply or became debilitated by severe vomiting. At this point they would present to hospital for intravenous fluid replacement. Vomiting tended to be intractable and refractory to the spectrum of antiemetic medication. The bathing behaviour was often commented on by the ward staff and noted in the case notes. Body temperature, in two cases, charted immediately following episodes of bathing, displayed low grade pyrexia. The patient's condition improved following a 24–48 hour intravenous fluid replacement regimen. The bathing behaviour then eased and they would be discharged home. Patients represented on a cyclical basis weeks or months later, often for many years.

Compulsive bathing behaviour

The compulsion to have multiple hot showers or baths was not part of a psychosis or obsessive-compulsive disorder. This was a learned behaviour which often did not present with the first few episodes of illness (as in L) but once established rapidly became a compulsion. The symptoms of nausea, vomiting, and abdominal pain would all settle within minutes in a hot bath or shower. Symptomatic relief was temperature dependent. The hotter the water, the better the effect. As the water cooled the symptoms returned. Two patients (X, Y) even scalded themselves in an attempt to have the water as hot as possible. These patients did not exhibit delusions or hallucinations which drove this behaviour, nor did they regard the showering as irrational and did not appear to resent it. Cessation of cannabis lead to cessation of the washing behaviour.

Differential diagnosis

Cyclical vomiting syndromes fall into two distinct categories: those with a physical basis and those of unknown aetiology. Hyperemesis gravidarum and some variants of porphyria are typical toxicities, with Addison's disease[5 6] an example of a metabolic cause.

Paediatric cyclical vomiting syndrome and psychogenic vomiting have unknown aetiologies. There has been much research into paediatric cyclical vomiting syndrome over the years. It has been associated with autonomic dysfunction,[7] epilepsy,[8] and behavioural problems.[9]Recent research has focused on it being a variant of migraine headache[10] or abdominal migraine.[11] We see this disorder as a separate disease state to that exhibited by our patients with no clear associations. Although both conditions exhibit a cyclical periodicity to their vomiting, they present at different ages with no evidence of substance abuse in the paediatric group. A further consideration was whether these patients were suffering cannabis withdrawal syndrome,[12 13] which occurs when cannabis is abruptly ceased, leading to a short self limiting syndrome of nausea, vomiting, insomnia, irritability, and anxiety. This was discounted on the basis that none of our patients had exhibited the desire or intent to cease cannabis. On the contrary, virtually all had increased their

Table 3 Clinical characteristics of the first five study subjects

Cannabis	Mr Y	Mrs X	Mr A	Mr Q	Mr R
Haematology (10×9/l)	Hb: 161 g/l WCC: 16.9 Neut: 15.2 Plat: 277	Hb: 156 g/l WCC: 11.5 Neut: 9.7 Plat: 261	Hb: 165 g/l WCC: 15.2 Neut: 13.0 Plat: 237	Hb: 146 g/l WCC: 14.0 Neut: 11.9 Plat: 239	Hb: 153 g/l WCC: 12.2 Neut: 10.6 Plat: 225
Biochemistry (mmol/l)	Sod: 140, K: 4.4, Cl: 99	Sod: 138, K: 4.1, Cl: 98	Sod: 148, K: 4.0, Cl: 109	Sod: 145, K: 3.5, Cl: 102	Sod: 144, K: 4.0, Cl: 107
Amylase	Normal	Normal	Normal	Normal	Normal
Hep/HIV	Neg	Neg	Neg	Neg	Neg
βhCG	–	Neg	–	–	–
C_2H_5OH	Nil	Nil	Nil	Nil	Nil
Porphyria	Neg	Neg	Neg	Neg	Neg
Urine drug screen (μg/l)	Cannabis only	Cannabis only	Cannabis only	Cannabis only	Cannabis only
Endoscopy (modified Savary-Miller criteria)	Grade 4 erosions	Normal	Grade 2 erosions	Normal	Grade 2 erosions
Colonoscopy	Neg	Neg	Neg	–	–
Abdominal ultrasound	Neg	Neg	Neg	Neg	Neg
Barium studies	Neg	Neg	Neg	Neg	–
Gastric emptying study	Grossly delayed	Normal	Normal	–	–
Multiple other investigations	Neg	Neg	Neg	Neg	Neg

Hb, haemoglobin; WCC, white cell count; Neut, neutrophils; Plat, platelets; Sod, sodium; Hep/HIV, hepatitis/human immunodeficiency virus; βhCG, beta human chorionic gonadotrophin (pregnancy test); C_2H_5OH, alcohol.

Table 4 Clinical characteristics of the remaining four study subjects and the case of psychogenic vomiting described in 1996 by de Moore and colleagues (Mr G*)[4]

Cannabis	Mr J	Miss K	Mr L	Mr E	Mr G*
Haematology (10×9/l)	Hb: 143 g/l WCC: 7.7 Neut: 3.9 Plat:234	Hb: 144 g/l WCC: 16.8 Neut: 14.4 Plat: 280	Hb: 169 g/l WCC: 6.7 Neut: 3.2 Plat: 233	Hb: 156 g/l WCC: 9.0 Neut: 5.1 Plat: 288	WCC: raised Neut: raised
Biochemistry (mmol/l)	Sod: 140, K: 4.7, Cl: 99	Sod: 143, K: 3.7, Cl: 103	Sod: 139, K: 4.2, Cl: 98	Sod: 143, K: 4.5, Cl: 106	Normal
Amylase	Normal	Normal	Normal	Normal	–
Hep/HIV	Neg	Neg	Neg	Neg	Neg
βhCG	–	Neg	–	–	–
C_2H_5OH	Nil	Nil	Nil	Nil	–
Porphyria	Neg	Neg	Neg	Neg	Neg
Urine drug screen (μg/l)	Cannabis only	Cannabis only	Cannabis only	Cannabis only	Cannabis only
Endoscopy (modified Savary-Miller criteria)	–	Grade 2 erosions	–	Normal	Mild reflux
Colonoscopy	–	Neg	Neg	–	–
Abdominal ultrasound	Neg	Neg	Neg	Neg	Neg
Barium studies	Neg	Neg	Neg	Neg	–
Gastric emptying study	–	–	–	–	–
Multiple other investigations	Neg	Neg	Neg	Neg	Neg

Hb, haemoglobin; WCC, white cell count; Neut, neutrophils; Plat, platelets; Sod, sodium; Hep/HIV, hepatitis/human immunodeficiency virus; βhCG, beta human chorionic gonadotrophin (pregnancy test); C_2H_5OH, alcohol.

marijuana consumption at the time of illness in an attempt to avail of its well documented antiemetic properties.

Psychogenic vomiting, first described by Hill in 1968,[3] as a separate entity to bulimia and anorexia nervosa, is a cyclical vomiting illness resurfacing in adult life from a tendency to vomit in childhood. Such patients commonly use illicit drugs or alcohol to control their illness.[4] The uncanny resemblance of our cases to a documented case of psychogenic vomiting is remarkable. The triad of chronic cannabis, cyclical vomiting, and compulsive bathing is indicative of a new syndrome with cannabis toxicity as a cause.

Clinical management

Patients tended to fall into two categories: those that scorned the idea that cannabis was the cause of their vomiting and those that accepted the concept. The former group often refused consent to treatment and follow up. The latter group was well motivated, happy to be consented, and punctually attended appointments. All patients, for legal and ethical reasons, were counselled to cease all cannabis abuse. Benzodiazepines, used for a maximum of two weeks at the time of initial presentation, were offered to patients to avert cannabis withdrawal syndrome[12 13] and psychological cravings. A member of the medical team provided an on call counselling service for any patient who had problems with abstinence. We attempted to review cases weekly for the first four weeks and then monthly for a minimum of 12 months. Psychological well being, state of health, and body weight were noted at each presentation. Each patient was required to give a consented urine drug test produced at the time of each consultation. The urine drug screen was titrated against the clinical course.

Pathophysiological considerations

Cannabis has traditionally been associated with an antiemetic action following acute ingestion. Here, however, we are presented with the paradoxical effect of hyperemesis in susceptible chronic cannabis smokers. Such a paradoxical response has only previously been demonstrated with acute toxicity to intravenous injection of crude marijuana extract.[14] We suspect that susceptible individuals may develop a reaction to cannabis following several years of exposure. The reasons for this are obscure. We also have difficulty explaining why, while this disease takes years to develop, it resurfaces within weeks of cannabis resumption, even after considerable periods of abstinence.

Cannabinoids have a long half life. They are extremely lipophilic and bind to cerebral fat.[15] Regular use is accumulative and this might give rise to toxicity in the sensitive patient. Cannabis is known to delay gastric emptying[16] and, interestingly, one of our patients (Y) had a severely delayed gastric emptying study at acute presentation while two others (X, A) had normal studies when investigated between bouts of illness.

Patients exhibited odd behaviour: they repeatedly bathed in hot water to abate their illness; they vomited severely and uncontrollably; they lost and gained kilos of weight in the presence and absence of cannabis, respectively; and they displayed a spectrum of autonomic symptoms from sweating, flushing, thirst, and alteration in body temperature to colicky abdominal pain.

One logical explanation for this might lie with marijuana's effect on the limbic system of the brain, particularly at the hippocampal-hypothalamic-pituitary level.[17–19] Cannabis toxicity may disrupt the balanced equilibrium of satiety, thirst, digestive, and thermoregulatory systems of the hypothalamus and this disruption might settle with hot bathing or showering. A hypothalamic action is further supported by evidence that chronic cannabis use affects the secretion of pituitary hormones, suppressing growth hormone, follicle stimulating hormone, and luteinising hormone, with documented pubertal arrest.[20 21] Cannabis cessation also results in these levels returning to normal with cessation of the disease state.[20 21] Pure hypothalamic disruption, however, does not fully explain the entire autonomic overload, suggesting other mechanisms at play. Crude cannabis is made up of over 60 different compounds.[22] Any one of these in toxic concentrations may be the culprit. The mechanism of action is equally complicated. It might be due to marijuana binding to CB1 receptor sites in the brain.[23] Alternatively, anandamide, with its action on vallinoid receptor function and thermal control, may have a role here.[23 24] The most recent research from Canada has shown that cannabidiol, in high concentrations, produces hyperemesis in house musk shrew models with lithium induced vomiting not acting through the CB1 receptor.[25] Clearly, further research, using models capable of emesis, is needed to detect the exact mechanism of this apparent toxic effect.

CONCLUSION

All 10 patients described in this paper were cyclical vomiters and chronic cannabis users. All long term sufferers (nine of 10) also exhibited an abnormal bathing behaviour during the acute phase of their illness. Symptoms resolved in seven patients with cannabis abstention, confirmed by urine drug screening. Three patients rechallenged themselves by resuming marijuana and relapsed within months. Two of these three abstained again and got better, while the third did not, and remains sick. These observations suggest a causative role for chronic cannabis abuse. Simultaneous induction of cyclical hyperemesis and compulsive bathing behaviour suggests a toxic response to one or more of the active ingredients of cannabis, presumably acting, at least in part, on the limbic system of the brain. Elucidation of the responsible pathways will require further research.

The compulsion to have multiple hot showers or baths exhibited by these chronic cases is not trivial. It is clinically important to both nurse and doctor as it ''flags'' these patients on the ward. Their ready identification should lead to a reduction in morbidity for the patient and cost to the health service. The consequences of this discovery bear further consideration. The paradoxical effect of its action must raise concerns about the long term tolerability of marijuana. Furthermore, it would also appear clinically prudent to exclude cannabis as an underlying cause in other cyclical illnesses, such as atypical abdominal and pelvic pain. Cannabis abstention, with urine drug screen monitoring, can be titrated against a clinical course. Finally, we feel that this disorder is an important differential diagnosis for unexplained vomiting, particularly in communities tolerant of cannabis. The diagnosis can be considered or discounted with the aid of an inexpensive consented drug screen.

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REFERENCES

1 **South Australia**. *Controlled substances act,* 1984.
2 **South Australia**. *Controlled substances act—expiation of simple cannabis offences,* 1987.
3 **Hill OW**. Psychogenic vomiting. *Gut* 1968;**9**:348–52.
4 **de Moore GM**, Baker J, Bui T. Psychogenic vomiting complicated by marijuana abuse and spontaneous pneumomediastinum. *Aust N Z J Psychiatry* 1996;**30**:290–4.
5 **Tobin MV**, Morris AL. Addisons disease presenting as anorexia nervosa in a young man. *Postgrad Med J* 1988;**64**:953–5.
6 **Tobin MV**, Aldridge SA, Morris AL, *et al*. Gastrointestinal manifestations of Addisons disease. *Am J Gastroenterology* 1989;**84**:1302–5.
7 **Rashed H**, Abell TL, Familoni BO, *et al*. Autonomic function in cyclical vomiting syndrome and classical migrane. *Dig Dis Sci* 1999;**44**(suppl 8):74–8S.
8 **Millichap JG**, Lombrosco CT, Lennox WG. Cyclical vomiting as a form of epilepsy in children. *Pediatrics* 1955;**15**:705–14.
9 **Forbes D**, Withers B, Silburn S, *et al*. Psychological and social characteristics and precipitants of vomiting in children with cyclical vomiting syndrome. *Dig Dis Sci* 1999;**44**(suppl 8):19–22S.
10 **Li BU**, Murray RD, Heitlinger LA, *et al*. Is cyclical vomiting syndrome related to migraine? *J Pediatr* 1999;**134**:567–72.
11 **Symon DN**, Russel G. The relationship between cyclical vomiting syndrome and abdominal migraine. *J Pediatr Gastroenterol Nutr* 1995;**21**:(suppl 1)S42–3.
12 **Crowley TJ**, MacDonald MJ, Whitmore EA, *et al*. Cannabis dependence, withdrawal and reinforcing effects amongst adolescents with conduct symptoms and substance use disorders. *Drug Alchol Depend* 1998;**50**:27–37.
13 **Haney M**, Ward AS, Comer SD, *et al*. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)* 1999;**141**:395–404.
14 **Vaziri ND**, Thomas R, Sterling M, *et al*. Toxicity with intravenous injection of crude marijuana extract. *Clin Toxicol* 1981;**18**:353–66.
15 **Devane WA**, Hanus L, Breuer A, *et al*. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;**258**:1946–9.
16 **McCallum RW**, Soykan I, Sridnar KR, *et al*. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind randomized study. *Aliment Pharmacol Ther* 1999;**13**:77–80.
17 **Pertwee RG**. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997;**74**:129–80.
18 **Childers SR**, Breivogel CS. Cannabis and endogenous cannabinoid systems. *Drug Alcohol Depend* 1998;**51**:173–87.
19 **Herkenham M**, Lynn AB, Little MD, *et al*. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A* 1990;**87**:1932–6.
20 **Mueller BA**, Daling JR, Weiss NS, *et al*. Recreational drug use and the risk of primary infertility. *Epidemiology* 1990;**1**:195–200.
21 **Copeland KC**, Underwood LC, Van Wyk JJ. Marijuana smoking and puberty arrest. *J Pediatr* 1980;**96**:1079–80.
22 **Watson SJ**, Benson JA jr, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine Report. *Arch Gen Psychiatry* 2000;**57**:547–52.
23 **Iversen L**. Cannabis and the brain. *Brain* 2003;**126**:1252–70.
24 **Zygmunt PM**, Petersson J, Andersson DA, *et al*. Vanilloid receptors on sensory nerves mediate the vasodilator actions of andandamide. *Nature* 1999;**400**:452–7.
25 **Parker LA**, Kwiatkowska M, Burton P, *et al*. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus(house musk shrew). *Psychopharmacology (Berl)* 2004;**171**:156–61.