BEF040001

Final report on

A Survey in Folate Deficiency and its Serious Consequences in Drug Abuser, with Emphasis on Cough Mixture Abuse

Supported by the Beat Drugs Fund Association

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Executive summary

1. Research objectives: To study the harmful effects of cough mixture abuse in terms of folate and vitamin deficiency.

2. Major findings: Up to 2/5 of cough mixture abusers may have significant folate deficiency. This side effect is unique to cough mixture abuse and not related to other lifestyle or personal factors. The effect cannot be predicted from simple blood tests or symptoms.

3. Conclusions: Many people with the habit of cough mixture abuse are at risk for severe damage to their brain and nervous systems. The side effects may come on suddenly and may lead to severe permanent disabilities. In pregnant mothers, this has the possibility to cause severe brain damage to the fetus.

Chapter 1. Objectives of study

Cough mixture abuse is an emerging problem in many Asian industrialized nations (1, 2). In the latest updates, it consists of over 1.8% - 3.1% of all registered substances abusers in Hong Kong. This may only be the tip of the iceberg and many young people conceive that cough mixture abuse is relatively safe and seldom seek voluntary help. This, together with the easy availability of over the counter prescriptions makes exact tallying of the extent abuse difficult. Furthermore, many cough mixture abusers may also be simultaneously experimenting or dependent on other substances, so that the exact statistics on the number of cough mixture abusers in the territory is likely to be grossly underestimated. However, data from the past five years showed at least over 200 active abusers. The profile is also characteristically male in their late 20s to early 30s (3).

There has been no systematic study on the health threats of cough mixture abuse, although it is known to cause psychological dependence, health and industrial hazards due to somnolence, and diagnostic severe dental caries due to the high sugar content of many of the mixtures (4). Despite the high incidence of abuse in Hong Kong and Asian countries, there were only scattered reports of lactate acidosis (5) and psychosis (6). One reason may be that abusers may present scattered to different medical units reducing the index of suspicion for a pattern of health effects. Furthermore, subtle damages may be easily overlooked in this population known for self-negligence and default, while major catastrophic damages were often attributed to other concomitant causes.

In 2003, our group reported the first short series in the world of the possible association between cough mixture abuse and severe folate deficiency accompanied by neurological defects (mainly peripheral neuropathy) in four consecutive in-patient cases in Queen Mary Hospital (7). The folate deficiency was sufficiently severe to cause megaloblastic changes in the peripheral blood and marrow in some cases. The neurological deficits were also crippling, although all cases achieved near full recovery with intensive vitamin support and physiotherapy rehabilitation. Using sophisticated metabolite analysis, we were able to show that the folate deficiency was genuine and leads to homocysteine (HC) accumulation. In some cases, spuriously low vitamin B12 levels may also be found, but the normal methylmalonic acid (MMA) levels excluded any block in the vitamin B12 metabolism. The report was well received and request for reprints were obtained from all continents except Africa and Anarctica.

Subsequently, our group also published further reports on possible effects of folate deficiency associated with cough mixture abuse in the central nervous system (8), and more seriously, in the developing neurotube of the infant (9). At this stage, there emerge a genuine need for a prospective project to really prove the specific association between cough mixture abuse and folate deficiency and to delineate in the prospective and quantifying manner, the extent and severity of the problem. After much work on multi-departmental and multi-cluster collaboration, ethics committee approval and government sponsorship was finally obtained for this prospective study.

The objectives of the study were therefore as follows:

To study the folate, vitamin B12, and metabolite levels of a group of cough mixture abusers and compared the results with that of a control group of abusers of the other drugs (10), so as to prove the specific biochemical effect of cough mixture abuse on folate metabolism. The study also hopes to elucidate the extent and severity of this biochemical side effect in a prospective manner.

The research hypothesis is therefore, that cough mixture abuse can lead to folate deficiency in a significant proportion of abusers and this is not seen in other types of substance abusers.

Chapter 2. Design of study

Patients were recruited from substance abuse assessment unit and three hospitals in the Kowloon West Cluster of Hospital Authority. In addition, four drug abuse outreach centers ran by Non-Government Organizations had kindly referred their clients to participate in this study.

1. Cross Centre, (Tung Wah Group of Hospitals)
   9/F TWGHs Fong Shu Chuen Social Service Building
   6 Po Man Street, Shaukeiwan, HK.

2. Hong Kong Lutheran Social Service
   The Evergreen Lutheran Centre
   2 Horse Shoe Lane
   Kwun Tong,
   Kowloon.

3. Hong Kong Christian Service
   PS33- Centre for psychotropic substance abusers
   G/F, 33 Granville Road
   Tsim Sha Tsui
   Kowloon.

4. Hong Kong Lutheran Social Service
   Cheer Lutheran Centre
   G/F, Shin Kwan House,
   Fu Shin Estate,
   Tai Po,
   NT.

All adult cough mixture abusers, who abused cough mixture continuously for at least two months with daily intake of more than 60mls were recruited. There was one subject who abused around 30 to 40 dextromethorphan tablets daily was also recruited.

With informed consent, patients were interviewed for demographic data and their history of drug abuse. The data was cross-referenced to the clinical records of the patient. All the data was based on voluntary admission and urine and blood toxicology studies were not performed at any point in time. A single blood sample was taken and sent to Queen Mary Hospital for assay of complete blood picture, vitamin B12, and folate. Specimens were frozen down and were subsequently thawed for batch assays of HC and MMA. Patients with abnormal results were recalled and referred to the medical unit of their hospital for further treatment.

The choice of metabolite assay was based on known pathways of vitamin B12 and folate metabolism and also our previous published report of marked elevated HC levels in cough mixture abusers with neurological deficit, confirming blockage in the folate metabolism pathway.

The ethics committee of both the Hong Kong West and the Kowloon East Clusters of the Hospital Authority approved the study design. The complete blood counts and red cell indices were recorded by standard automated cell counters (Gen-S, Beckman Coulter, FL and Advia 120, Bayer Diagnostics, NY). Peripheral film and marrow biopsies were examined using standard morphological criteria, and vitamin B12 and folate levels were assayed using enzyme immunoassay (Access system, Beckman Coulter, FL). Plasma methylmalonic Acid (MMA) levels were measured by gas chromatography-mass spectroscopy (GC-MS) with isotope dilution and plasma total homocysteine levels by a fluorescence polarization immunoassay on the Abbott IMx system (Abbott Laboratories, Abbott Park, IL, USA). The laboratories assessing the hematological and biochemical data were blinded to the nature of the specimens and to each other's results. All results were analyzed at the conclusion of the study using SPSS 11.0 software (Chicago, IL, USA).

The period of study was initially stipulated to be 1 July 2004 to 1 July 2005, but was extended to 31 December 2005 due to slow accrual. The first 99 patients joined the study on a voluntary unrewarded basis. However, with stalling the recruitment of the study, it was jointly decided by the investigators and Beat Drugs Fund that $100 transport charge may be issued to subsequent participants to compensate for the time and effort taken by the subjects. However, for the last 3 months of the study, only 8 further subjects could be recruited and only 4 accepted travel re-imbursement illustrating that money was not the main concern for potential subjects opting out of the project.

Chapter 3. Research data and statistical analysis

Demographic data: A total of 107 subjects were recruited. There were 76 men and 31 women and the median age was 32.1 years (range 21 to 45 and one case age 86). A single control case who claimed to be an alcohol abuser was an elderly woman of 86 years of age. There were 57 cases in the cough mixture abuser group and 50 cases in the control group.

The drug abuser and control groups were first compared directly against each other and the data is shown in table one. The detailed background information of all cases is shown in Appendix.

The subjects may be classified into three groups:

1. Abusers of cough mixture only: n=37 (consisting of 21 who abused codeine only, 11 dextromethorphan only, 5 both codeine and dextromethorphan)
2. Abusers of cough mixture (either codeine or dextromethorphan) and other psychotropic substances/alcohol: n=20
3. Abusers of psychotropic substances/alcohol (other than cough mixture) only: n=50

Groups 1-2 were analyzed together as the study group to allow sufficient statistical power.

Table 1.

Attribute	Overall	Study group (Cough)	Control group (Psychotropics)	p value	RR (95% CI)
Male vs Female	*76 vs. 31*	*45 vs. 12*	*31 vs. 19*	*0.043*	*1.277 (1.0-1.6)*
Median age (range)	*32.1 (18-55)*	*31.2 (19-49)*	*33.5 (18-55)*	*0.26*	*NA*
No. of single	*66*	*43*	*23*	*0.048*	*NA*
married and	*14*	*5*	*9*		
divorced	*21*	*9*	*12*		
No. of employed and	*27*	*17*	*10*	*0.38*	*NA*
unemployed	*76*	*40*	*36*		
No. of living alone,	*66*	*40*	*26*	*0.001*	*NA*
living with family,	*22*	*14*	*8*		
homeless and	*13*	*2*	*11*		
living with friends	*2*	*1*	*1*		

The drug abuse data of the cough mixture and control group was then analyzed.

Among the 57 cough mixture abusers, 37 were pure cough mixture abusers,

while 20 had concomitant other substance abuse as follows: Benzodiazepam=12, heroin=3, ice=1, alcohol=1, cannabis=1, ecstasy =1others or undeclared =2. Both codeine (n=33) and dextromethorphan (n=19) were used among cough mixture abusers, including combined usage in 5 cases and use of codeine "pills" in one case.

The median daily volume consumed was 290 ml (range 50- 1500ml).

Among the control group, the abused substance included: heroin =22, benzodiazepam=7, alcohol=9, ketamine =7, cannabis=6, ecstasy=5, ice=4, volatile solvent =1, others =2. Poly-substance abuse was reported in 15 cases.

The biochemical and hematological data was analyzed between the two groups.

Table 2.

Attribute	Study group (Cough)	Control group (Psychotropics)	p value
Red cell folate	*247 +/-28*	*337 +/- 36*	*0.001*
Serum Vitamin B12	*265 +/-13*	*393 +/- 23*	*0.001*
Serum Folate	*6.2 +/- 0.4*	*7.6 +/-0.56*	*0.046*
Homocysteine	*21.1 +/- 1.3*	*24.7 +/- 2.1*	*0.098*
Methylmalonic acid	*0.41 +/- 0.14*	*0.26 +/- 0.02*	*0.398*

Legend: Red blood cell folate level in ug/l (normal >164);
vitamin B12 level in mg/l (normal 170-810);
serum folate (normal >3);
HC: normal value 18.6-30.2 umol/l;
methylmalonic acid normal value <0.38 umol/l.

Cough mixture abusers, therefore showed hematologically significantly lower red cell folate and serum vitamin B12 levels compared with other substance abusers. Further analysis showed that there was no difference in these apparent hematological defects between codeine and dextromethorphan abusers. A high incidence of folate deficiency was interestingly not seen in heroin abusers, who did not volunteered to cough mixture abuse, which was surprising given that both active substances belong to the same class of chemicals. Within the whole group, there was no statistically significant difference in terms of HC and MMA levels.

For patients *with* versus those *without* deficiencies, the subdivisions and metabolite analysis were as follows:

Table 3.

Attribute	Cough vs. others (no. and % of patients with deficiencies)	p value	95% CI
Low Red cell folate n=27	22 (39%) vs. 5 (10%)	0.004 (RR=4.6)	1.6-13.2
Low Vitamin B12 n=12	10 (17%) vs. 2 (4%)	0.033 (RR=4.3)	1.06-19.7
Low serum folate n=10	7 (12%) vs. 3 (6%)	0.33	NA

Table 4.

Attribute	HC (with deficiencies vs. without deficiencies)	p value
Low Red cell folate n=27	31.1 vs. 20.3	0.001
Low Vitamin B12 n=12	30.7 vs. 20.7	0.042
Low serum folate n=10	33.9 vs. 20.7	<0.001

Table 5.

Attribute	MMA (with deficiencies vs. without deficiencies)	p value
Low Red cell folate n=27	0.57 vs. 0.25	0.476
Low Vitamin B12 n=12	0.33 vs. 0.34	0.58
Low serum folate n=10	0.26 vs. 0.35	0.345

Table 6.

Attribute	B12 (with deficiencies vs. without deficiencies)	p value
Low Red cell folate n=27	8/27 vs. 4/78	0.001 RR=6.7 (2.2-20.5)
Low Vitamin B12 n=12	NA	NA
Low serum folate n=10	1 /10 vs. 11/95	0.68

In terms of symptomatology, only the cough mixture group was actively questioned. They reported psychotic symptoms n=25, numbness n=23,

limb weakness n=11, dizziness n=6, dental carries n=49. Among the symptoms, numbness was associated with a significant larger amount of consumption of cough mixture and lower B12, while psychotic symptoms was associated with low B12, higher HC and more consumption.

There was no difference in folate levels or incidence of folate deficiency between patients with and without any voluntarily reported symptoms.

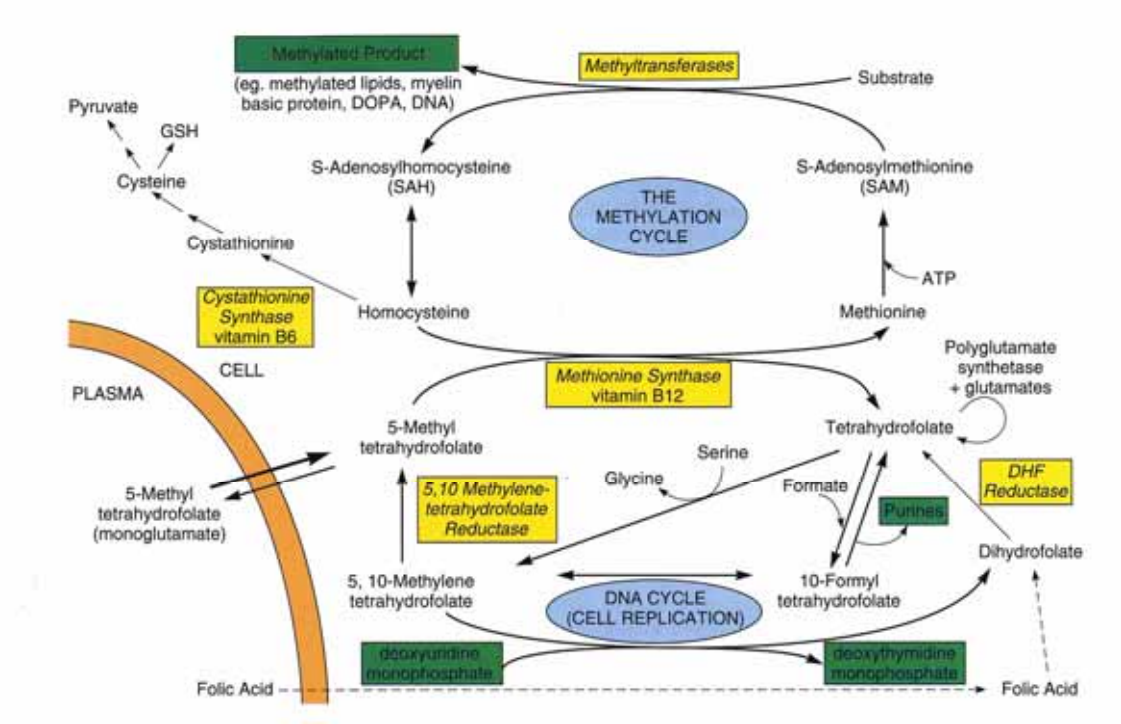
Chapter 4. Interpretation of data

Our data with a sound control group and blinded analysis of samples clearly showed that cough mixture abuse is associated with a high incidence of folate deficiency (red cell folate deficiency was found in 38.6% of patients who abused cough mixture). This is unrelated to the voluntary volume of abuse, concomitant drugs and the type of cough suppressant used (dextromethorphan or codeine). It was also unrelated to the sugar consumption associated with cough mixture since at least one deficient patient took codeine phosphate pills (11). Unlike in alcoholics, an intestinal malabsorption mechanism is unlikely to be involved (12).

Many patients, however, showed low vitamin B12 levels. Our previous result have shown that this is a spurious low level due to severe folate deficiency and was documented by normal MMA level with high HC levels. In this prospective cohort, the relationship between low folate and vitamin B12 level was also strong (13). Furthermore, patients with folate deficiency and Vitamin B12 deficiency has high HC levels, characteristic of folate pathway blockade, but unincreased MMA levels that do not support any additional block in vitamin B12 metabolic pathways. The HC levels in our study were all well above the reference levels, since fresh samples were not available for analysis. During the transport of specimens from the peripheral centers to the central analysis laboratory, HC was continuously released from red cells before separation of serum can be done. Nevertheless, this affects both normal and abnormal samples and our previous observation of increased HC in folate deficient and spurious low

B12 cases can still be demonstrated.

Chart 1.



In humans, only two enzymatic reactions are dependent on vitamin B12. MMA is converted to succynyl-CoA using B12 as a cofactor. Deficiency can lead to increased MMA. Secondly, HC is converted to methionine by using B12 and folate as a cofactors, and, a deficiency lead to increased HC levels. Both the nervous system and marrow requires a constant supply of glucose and DNA building blocks, which involve methylation processes, requiring folate and vitamin B12. The biochemical basis of the interrelationship between folate and cobalamin is the maintenance of nucleic acid synthesis and the methylation reactions. The lack of substrate for nucleic acid synthesis explains the megaloblastic anemia and nuclear cytoplasmic dysynchrony seen in the marrow of B12 and folate deficient

patients. The neuropathy and central nervous system effects are more difficult to explain. The *de novo* synthesis of methionine requires B12, which serves the transfer of the methyl group to HC. In turn, methionine is required in the synthesis of S-adenosylmethionine (SAM). Upon transfer of its methyl group, SAM is converted to S-adenosylhomocysteine (SAH), and hydrolyzed to HC and adenosine. If HC accumulates, it will be rapidly metabolized to SAH, which competes with SAM for the active site on the methyltransferase enzyme protein. The brain relies on maintaining the concentration of SAM which maintains the methylation reactions and its inhibition causes neuropathy. In case of folate or B12 deficiency, the methionine synthetase reaction is severely impaired, since B12 is needed for the methyl donation from 5 methyltethrahydrofolate in tetrhahydrofolate. Folate promotes the remethylation of HC- a cytotoxic sulfur-containing amino acid that can induce DNA strand breakage, oxidative stress and apoptosis. The oxidation of homocysteine to homocysteic acid is the potential explanation of the dangerous effect of HC. In fact, HC is a mixed excitatory agonist preferentially at N-Methyl- D-Aspartate (NMDA) receptors, whose hyper or abnormal activation cause release of cellular proteases and eventual cell death.

Although our study showed that folate deficiency is prevalent among cough mixture abusers, it failed to identify any risk factors for such deficiency. Furthermore, such deficiency also exists in a lower scale in other substance abusers. Hence, it is possible that some individuals may be at increased genetic risk of such metabolic defects (14). Furthermore, our results also showed that clinical and laboratory parameters are poor guide to the severity

of folate deficiency in at risk populations. Hence, prospectively vitamin screening and perhaps supplementation may be needed (15, 16).

Our study focused on patients without clinically overt symptoms, and again, symptomatology was poor guide to identify at risk cases. It must be remembered, however, that the study is voluntary in nature and the cough mixture and clinical history volunteered by patients may not be entirely accurate (17). Furthermore, presenting them to the study represent some form of self-selection and it is possible that the most severely deficient cases have been entirely missed. Nevertheless, in our limited experience, the finding of metabolite deficiency does constitute an impetus for patients to volunteer more symptoms subsequently and agreed to control their substance abuse behavior.

Chapter 5. Recommendations from research findings

Without repeating aforementioned points and proven facts of our findings, the following assertions and recommendations can be endorsed by the investigators:

The potential effects of cough mixture abuse causing severe folate deficiency resulting in life threatening, permanently disabling and fetus harming neurological defects MUST be made known to public, especially young individuals of employment and reproductive age. The potential side effects so far included: wheelchair bound weakness, convulsions requiring intensive care, deformity of babies, and complete numbness of limbs resulting in inability to work and self care.

The possibility of this deficiency should be made known to hematologists, neurologists, dietitians and psychiatrists, so that cases can be properly diagnosed, triaged, referred and treated.

Screening for vitamin deficiency should be prospectively undertaken at all substance abuse clinics both to collect a larger database to substantiate our findings, and more importantly, prevent reversible neurological defect and provide more quitting incentive to at risk individuals. It is emphasized again that the main biochemical defect is folate deficiency, which can cause spuriously low vitamin B12 levels, detected with the same package of biochemical tests in most laboratories.

Further funding may be considered to look into the scientific aspects of such association between folate deficiencies and cough mixture abuse using animal models and metabolite analysis to pinpoint the exact stage of blockage of metabolism (18), so that better remedy is available to severe cases.

The limitation of the study included the recruitment catchment which is entirely voluntary. Hence, severe abusers may elect not to turn up. Furthermore, the drug usage is self-confessed and may not be accurate. We did not have the manpower for immediate analysis of fresh blood, nor the time and money to analyze the exact pathways of folate inhibition. There is also no structured longitudinal follow up of the subjects to see if any abstinence from abuse will lead to metabolic recovery.

Appendix: Detailed information of the subjects

Table A1.

Serial no.	Sex	Age	Marital status	Employment status	Type of accommodation
1	M	22	Single	Unemployed	Living alone
2	M	46	Divorced	Employed	Living alone
3	M	30	Single	Unemployed	Homeless
4	M	48	Divorced	Unemployed	Living with family
5	M	29	Single	Unemployed	Homeless
6	M	27	Single	Unemployed	Living alone
7	F	31	Single	Unemployed	Homeless
8	M	31	Single	Unemployed	Homeless
9	F	46	Divorced	Unemployed	Living with friends
10	M	21	Single	Unemployed	Living alone
11	M	28	Single	Unemployed	Living with family
12	F	19	Single	Employed	Homeless
13	F	30	Single	Employed	Living alone
14	M	55	Divorced	Unemployed	Living alone
15	M	34	Single	Unemployed	Living with family
16	M	29	Divorced	Unemployed	Living alone
17	M	28	Single	Unemployed	Living alone
18	F	86	Widowed	Unemployed	Homeless
19	M	25	Divorced	Unemployed	Living with family
20	F	46	Divorced	Unemployed	Living alone
21	M	28	Single	Employed	Living alone
22	F	27	Single	Employed	Living with family
23	F	23	Single	Employed	Living alone
24	M	29	Single	Employed	Living alone
25	M	29	Single	Unemployed	Living alone
26	F	41	Divorced	Employed	Living alone
27	F	18	Single	Unemployed	Living alone
28	M	39	Single	Unemployed	Living with friends
29	M	31	Married	Unemployed	Living alone
30	M	30	Single	Unemployed	Living alone
31	M	29	Single	Unemployed	Living alone
32	F	24	Married	Employed	Living alone
33	M	29	Married	Employed	Living alone
34	F	19	Single	Unemployed	Living alone

Serial no.	Sex	Age	Marital status	Employment status	Type of accommodation
35	M	19	Single	Unemployed	Living alone
36	F	46	Single	Unemployed	Living with family
37	M	44	Divorced	Unemployed	Living with family
38	F	33	Single	Unemployed	Homeless
39	M	43	Married	Unemployed	Living alone
40	M	32	Single	Unemployed	Living alone
41	M	29	Single	Unemployed	Homeless
42	F	20	Single	Unemployed	Living alone
43	M	29	Married	Unemployed	Living alone
44	M	36	Single	Unemployed	Living with family
45	M	31	Single	Unemployed	Living alone
46	M	40	Married	Unemployed	Living alone
47	F	28	Married	Employed	Living alone
48	M	49	Divorced	Unemployed	Living with family
49	F	32	Married	Employed	Living alone
50	M	48	Divorced	Unemployed	Living with family
51	M	26	Married	Employed	Living alone
52	F	46	Divorced	Unemployed	Living with family
53	F	24	Single	Unemployed	Living alone
54	F	18	Single	Employed	Living alone
55	M	29	Single	Unemployed	Living with family
56	M	26	Single	Unemployed	Living alone
57	M	23	Single	Unemployed	Living alone
58	F	37	Divorced	Unemployed	Living alone
59	M	28	Single	Employed	Living alone
60	M	27	Single	Unemployed	Living with family
61	F	31	Single	Employed	Living alone
62	F	43	Divorced	Employed	Living with family
63	M	34	Single	Unemployed	Living alone
64	M	28	Single	Unemployed	Living alone
65	F	29	Single	Unemployed	Homeless
66	M	29	Single	Unemployed	Living alone
67	M	23	Single	Unemployed	Living alone
68	M	31	Married	Unemployed	Living alone
69	M	37			
70	M	26	Single	Unemployed	Living with family
71	M	35	Single	Unemployed	Living alone

Serial no.	Sex	Age	Marital status	Employment status	Type of accommodation
72	M	41	Divorced	Unemployed	Living alone
73	M	31	Single	Unemployed	Living alone
74	F	31			
75	M	20	Single	Unemployed	Living alone
76	M	29	Single	Employed	Living with family
77	M	26	Single	Unemployed	Living alone
78	F	25	Single	Employed	Living alone
79	M	20	Single	Employed	Living alone
80	M	29	Single	Unemployed	Living alone
81	M	35	Single	Unemployed	Living alone
82	M	28	Single	Unemployed	Living alone
83	M	23	Single	Unemployed	Living with family
84	M	29	Single	Unemployed	Living with family
85	F	49	Divorced	Unemployed	Living with family
86	M	29	Single	Unemployed	Homeless
87	M	34			
88	M	36			
89	M	35	Married	Unemployed	Living alone
90	M	32	Single	Employed	Homeless
91	F	25	Married	Employed	Living alone
92	F	36	Single	Employed	Living alone
93	M	26	Single	Employed	Living with family
94	M	31	Single	Unemployed	Living with family
95	M	42	Married	Employed	Living alone
96	M	32	Single	Unemployed	Living alone
97	M	28	Single	Employed	Living alone
98	M	35	Single	Unemployed	Living with family
99	M	39	Divorced	Unemployed	Homeless
100	M	24	Single	Unemployed	Living alone
101	M	29	Single	Unemployed	Living alone
102	M	45	Married	Employed	Living alone
103	M	24	Divorced	Unemployed	Living alone
104	F	43	Single	Unemployed	Living alone
105	F	30	Divorced	Unemployed	Homeless
106	M	36	Divorced	Unemployed	Living alone
107	M	37	Divorced	Unemployed	Living alone

Table A2.

Serial no.	Drug group	Whether cocktailed	Cough mixture	Daily amount of cough mixture consumed (ml)	Psychiatric diagnosis
1	5		N		ketamine intoxication
2	5		N		alcohol dep
3	5		N		heroin dep
4	5		N		alcohol dep
5	5		N		alcohol dep
6	5		N		psychosis
7	5		N		heroin dep
8	5		N		depression
9	5		N		adjustment disorder
10	5		N		psychosis
11	5		N		heroin dep
12	5		N		polysubstance abuse
13	5		N		alcohol dep
14	5		N		alcohol dep
15	2		Y		cough mixture abuse
16	2		Y		cough mixture abuse
17	3	Y	Y		cough mixture abuse
18	5		N		alcohol dep
19	2		Y		cough mixture abuse
20	5		N		benzodiazepam intoxication
21	3	Y	Y		cough mixture abuse
22	5		N		depression
23	5		N		psychosis
24	4	Y	Y		psychosis
25	5		N		heroin dep
26	4	Y	Y		polysubstance abuse
27	5		N		psychosis
28	3	Y	Y		psychosis
29	5		N		heroin dep
30	2		Y		cough mixture abuse
31	5		N		heroin dep
32	5		N		heroin dep
33	5		N		heroin dep
34	5		N		schizophrenia
35	2		Y		cough mixture abuse

Serial no.	Drug group	Whether cocktailed	Cough mixture	Daily amount of cough mixture consumed (ml)	Psychiatric diagnosis
36	4	Y	Y		psychosis
37	5		N		heroin dep
38	5		N		heroin dep
39	5		N		heroin dep
40	5		N		heroin dep
41	5		N		heroin dep
42	1		Y		cough mixture abuse
43	5		N		heroin dep
44	5		N		heroin dep
45	2		Y		cough mixture abuse
46	5		N		heroin dep
47	5		N		heroin dep
48	5		N		heroin dep
49	5		N		heroin dep
50	5		N		heroin dep
51	5		N		heroin dep
52	5		N		heroin dep
53	5		N		psychosis
54	4		N		cough mixture abuse
55	4	Y	Y		heroin and cough mixture abuse
56	1		N		cough mixture abuse
57	5		N		heroin dependence
58	4	Y	Y		heroin and cough mixture abuse
59	2		Y		cough mixture abuse
60	2		Y		cough mixture abuse
61	3	Y	Y	100	cough mixture abuse
62	1		Y	250	cough mixture abuse
63	1		Y	250	cough mixture abuse
64	1		Y	1000	cough mixture abuse
65	1		Y	400	cough mixture abuse
66	2		Y	800	cough mixture abuse
67	1	Y	Y	300	cough mixture abuse
68	3		Y	300	cough mixture abuse
69			Y		cough mixture abuse

Serial no.	Drug group	Whether cocktailed	Cough mixture	Daily amount of cough mixture consumed (ml)	Psychiatric diagnosis
70	1		Y	200	cough mixture abuse
71	1		Y	360	cough mixture abuse
72	3		Y	300	cough mixture abuse
73	4		Y		cough mixture abuse
74			N		cough mixture abuse
75	4	Y	Y	300	cough mixture abuse
76	1+2		Y	1500	cough mixture abuse
77	1+2		Y	50	cough mixture abuse
78	1		Y	120	cough mixture abuse
79	1+2		Y	200	cough mixture abuse
80	2		Y	300	cough mixture abuse
81	1		Y	360	cough mixture abuse
82	1		Y	120	cough mixture abuse
83	1		Y	120	cough mixture abuse
84	3		Y	120	cough mixture abuse
85	1		Y	120	cough mixture abuse
86	5		N		alcohol dep
87			Y		others
88			N		others
89	1		Y	240	cough mixture abuse
90	1		Y	240	cough mixture abuse
91	1		Y	120	cough mixture abuse
92	1		Y	240	cough mixture abuse
93	3		Y	120	cough mixture abuse
94	3	Y	Y		polysubstance abuse
95	1+2		Y	500	cough mixture abuse
96	3	Y	Y	120	polysubstance abuse
97	3	Y	Y	180	polysubstance abuse
98	3	Y	Y	120	polysubstance abuse
99	5	Y	Y	0	heoin dep
100	1		Y	300	cough mixture abuse
101	2		Y	500	cough mixture abuse
102	1		Y	120	cough mixture abuse
103	1+2		Y	180	cough mixture abuse
104	5		N		polysubstance abuse
105	5		N		canisbis abuse

Serial no.	Drug group	Whether cocktailed	Cough mixture	Daily amount of cough mixture consumed (ml)	Psychiatric diagnosis
106	1		Y	240	cough mixture abuse
107	5		N		ice (amphetamine abuse)

Legend for Drug Group: 1.codeine only, 2.dextromethorphan only, 3.codeine plus other psychoactive substances, 4.dextromethophan plus other psychoactive substances, 5. psychoactive substances only

Table A3.

Serial no.	Ecstasy	Cannabis	Ketamine	Heroin	Volatile	Alcohol	Ice	Benzo	Others
1			Y						
2						Y			
3				Y				Y	
4						Y			
5						Y			
6		Y	Y						
7				Y				Y	
8			Y	Y					
9								Y	
10		Y	Y						
11				Y				Y	
12	Y	Y	Y				Y	Y	
13						Y			
14						Y			
15									
16									
17						Y			
18						Y			
19									
20								Y	
21	Y						Y		
22						Y			
23			Y						
24								Y	
25	Y	Y	Y	Y					
26									Y
27	Y								
28				Y				Y	
29				Y					
30									
31				Y					
32				Y					
33				Y					
34							Y		
35									
36		Y						Y	

Serial no.	Ecstasy	Cannabis	Ketamine	Heroin	Volatile	Alcohol	Ice	Benzo	Others
37				Y					
38				Y					
39				Y					
40									
41									
42									
43				Y					
44				Y					
45									
46				Y					
47				Y					
48				Y					
49				Y					
50				Y					
51				Y					
52				Y					
53	Y						Y		
54	Y	Y			Y				
55				Y				Y	
56									
57				Y					
58				Y				Y	
59									
60									
61								Y	
62									
63									
64									
65									
66									
67								Y	
68									
69									
70									
71									
72									
73									

Serial no.	Ecstasy	Cannabis	Ketamine	Heroin	Volatile	Alcohol	Ice	Benzo	Others
74									
75								Y	
76									
77									
78									
79									
80									
81									
82									
83									
84									
85									
86						Y			
87									Y
88									Y
89									
90									
91									
92									
93									
94									Y
95									
96								Y	
97								Y	
98								Y	
99								Y	
100									
101									
102									
103									
104						Y		Y	
105		Y							
106									
107							Y		

Table A4.

Serial no.	Psychiatric complications	Numb	Limbs weakness	Dizziness	Dental carries	Medical diagnosis
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						Derranged LFT
15	Y	Y			Y	
16	Y				Y	
17	Y				Y	
18						
19	Y	Y			Y	IHD
20						
21	Y	Y				
22						
23						
24	Y	Y	Y	Y	Y	
25						
26	Y			Y		
27						
28	Y					
29						
30					Y	
31						
32						
33						
34						
35					Y	
36	Y	Y	Y		Y	
37						
38						

Serial no.	Psychiatric complications	Numb	Limbs weakness	Dizziness	Dental carries	Medical diagnosis
39						
40						
41						
42						
43						
44						
45					Y	
46						
47						
48						
49						
50						
51						
52						
53						
54		Y		Y	Y	
55		Y			Y	
56						
57						
58		Y			Y	
59					Y	
60		Y			Y	
61						
62	Y	Y			Y	
63					Y	
64	Y	Y			Y	
65		Y			Y	
66	Y	Y	Y	Y	Y	Recurrent limbs weakness
67					Y	
68					Y	
69					Y	
70	Y				Y	
71	Y	Y	Y	Y	Y	
72	Y	Y	Y		Y	
73	Y					
74						
75					Y	
76	Y	Y			Y	

Serial no.	Psychiatric complications	Numb	Limbs weakness	Dizziness	Dental carries	Medical diagnosis
77						
78					Y	
79					Y	
80					Y	
81					Y	
82					Y	
83						
84	Y				Y	
85					Y	
86						
87						
88						
89	Y	Y	Y		Y	
90		Y	Y		Y	
91					Y	
92					Y	
93	Y				Y	
94	Y				Y	
95					Y	
96		Y			Y	
97	Y	Y	Y		Y	
98					Y	
99						
100						
101	Y	Y	Y		Y	
102	Y				Y	
103	Y				Y	
104						
105						
106		Y	Y		Y	
107						

Table A5.

Serial no.	Red cell folate 164	Serum B12 180	Serum folate 3	HC 12
1	202.89	660	6.8	23.7
2	265.94	392	9.9	26.3
3	119.97	362	7.2	35.5
4	1188.04	850	20	24.8
5	260.89	542	12.3	22
6	242.98	227	9	21.2
7	148.8	791	8.4	18.6
8	330.43	477	9.9	22.45
9	205.34	275	3.3	22.73
10	252.16	256	3.9	33.14
11	313.5	316	5.6	24.32
12		666	17.7	13.11
13	369.7	471	8.7	22.43
14	429.74	388	6.6	40.48
15	160.09	171	4.4	29.14
16	100.24	224	6.3	33.13
17	265.73	166	5.3	26.32
18	306.38	332	7.1	20.12
19	138.81	234	4.9	32.53
20	377.33	416	10.4	19.25
21	249.22	205	6.6	25.52
22	280.25	316	6.6	16.24
23	344.27	209	6.2	NA
24	167.64	188	5.5	20.41
25	191.97	382	5	20.43
26	217.3	337	8.1	QNS
27	203.23	398	5.4	31.97
28	1112	271	7.9	26.31
29	493.58	402	17.9	22.65
30	893.72	396	6.2	24.89
31	921	238	6.4	28.7
32	309.93	475	9	16.04
33	311.27	440	11.4	16.3
34	177.71	322	4.5	15.5
35	121.13	401	3.2	34.3
36	144.52	294	2.6	25.9
37	224.21	409	6.5	19.73
38	207.33	343	5.2	18.15

Serial no.	Red cell folate 164	Serum B12 180	Serum folate 3	HC 12
39	361.86	797	11.5	15.87
40	135.34	203	2.5	24.21
41	960.57	277	3.8	30.09
42	245.12	434	3.9	19.78
43	212.14	209	2.4	59.1
44	203.93	223	5	24.78
45	325.66	444	6.8	22.92
46	390.04	394	7.9	24.81
47	517.7	435	7.2	18.83
48	495.98	461	7.6	25.88
49	184.34	248	3	23.85
50	1014.55	352	7.1	23.39
51	325.1	304	5.6	27.87
52	356.16	324	7.9	19.04
53	254.38	261	4.8	17.91
54				16.15
55	223.57	337	2.7	21.25
56	240.29	312	5.4	10.1
57	170.85	224	8.3	21.43
58	170.85	189	6.8	12.9
59	147.54	201	3.6	21.7
60	162.39	192	4.2	19.7
61	225.8	269	4.9	10.4
62	272	146	11.8	10.8
63	250	596	5.1	11.9
64	116	177	4.5	18.7
65	83	235	11.6	17.8
66	63	158	5.1	20.2
67	231	406	9.4	10.9
68	300.15	171	9.8	12.1
69	201.91	263	7.6	17.6
70	872	229	10.5	21
71	133.68	443	2.6	48
72	912	345	18.3	8.3
73	125.22	175	6.2	12.5
74	216.89	325	5.1	18.2
75	320.55	301	5.4	12.3
76	111.43	127	4.4	22.1
77	246.46	258	5.2	12.7

Serial no.	Red cell folate 164	Serum B12 180	Serum folate 3	HC 12
78	201.66	362	10.3	13
79	229.77	272	12.4	14.8
80	201.61	228	10.3	13.1
81	79.37	148	4.2	52.4
82	182.13	312	6.1	21.7
83	300.47	227	3.6	12.4
84	152.1	333	7.7	17.2
85	218.59	191	7.5	20
86	260.89	542	12.3	15.4
87	57.27	130	0.98	102
88	110.99	102	1.2	55.4
89	125.16	110	8.5	24.2
90	127.86	236	6.6	15.2
91	233.79	195	4.4	15.2
92	202.64	358	4.9	13.9
93	191.72	202	7.8	18.2
94	150.18	200	5.2	23.6
95	121.88	167	2.9	NA
96	112.31	193	3.8	NA
97	308.13	275	5	NA
98	201.92	186	3	21.2
99	356.6	480	6.3	23.6
100	181.93	406	2.9	30.8
101	117.17	241	7.8	23.1
102	158.88	237	2.1	51.5
103	273.23	349	4.2	14.9
104	316.27	446	5.8	15.1
105	331.36	448	7.5	10.2
106	326.24	200	5.1	18.2
107	375.71	264	3.8	17.9

Table A6.

Serial no.	MMA 0.38	Hb	MCV	MCH	WBC	Plt
1	0.11	15	94.4	32	9.4	274
2	0.21	14.8	99.2	31.4	2	134
3	0.19	12.7	106.3	31.9	3.88	183
4	0.26	8.5	109.8	34.8	2.5	109
5	0.21	13.7	95.5	31.3	13.73	270
6	0.21	15	90.3	30.4	8.2	285
7	0.2	11.6	95	30.2	1.81	203
8	0.29	14.9	86.2	30.1	4.84	287
9	0.03	14	91.1	30.7	8.3	314
10	0.18	13.9	91.9	30.8	8.7	271
11	0.06	16	89.9	30.4	8.4	260
12	0.09	NA	NA	NA	NA	NA
13	0.38	13.8	104	34.2	5.1	199
14	0.13	17.1	94.3	32.1	7.19	248
15	0.19	15.6	90.7	30.6	10.3	226
16	0.26	13.2	94.2	31.9	10.6	311
17	0.33	15.7	96.6	33.5	8.2	377
18	0.47	12.3	86.5	28.2	7.1	214
19	0.43	15.3	87.3	30.6	7.1	233
20	0.22	12.6	90.6	30.2	8.5	273
21	0.16	15.6	90.7	31.2	10.1	113
22	0.08	13.2	85.6	29.1	4.8	177
23	na	11.5	91.6	31.1	10.6	200
24	0.29	14.4	97.9	32.7	6.4	212
25	0.21	12.9	67.1	21.7	5.8	212
26	0.3	13.4	94.4	31.5	7	359
27	0.09	14.1	90	29.8	6.33	399
28	0.28	12.7	89.2	30.5	6	260
29	0.16	14.4	93.2	31.7	7.7	197
30	0.23	15.1	93.8	31.7	6.7	208
31	0.27	15.5	86.4	29.7	4.6	51
32	0.39	12.6	86.9	29.6	5.3	216
33	0.34	12.9	88.5	30	11.8	228
34	0.16	11.7	88.3	29.9	6.8	220
35	0.16	15.6	97.6	32.1	4.4	171
36	0.18	11.9	96.2	32.6	10.3	544
37	0.27	13.2	89.2	30.8	9.5	213
38	0.29	11	62.1	19.8	12.4	371

Serial no.	MMA 0.38	Hb	MCV	MCH	WBC	Plt
39	0.22	13.1	97.2	34.6	7.3	209
40	0.29	14.6	95.7	32.9	5.6	287
41	0.21	14.7	81.8	27.6	8.32	151
42	0.44	10.8	73.2	23.3	6.59	361
43	0.42	12.3	69.4	22.8	6.43	243
44	0.24	14.9	94.8	31.5	7.5	236
45	0.18	13.7	81.7	26.8	9.9	427
46	QNS	15.8	96.9	33.9	6	158
47	0.29	15.4	95.4	32	9	262
48	0.38	15	94.4	31.5	10	262
49	0.37	13.2	96.2	33.3	7.4	196
50	0.31	12.8	108.8	37.1	5.4	152
51	QNS	16.5	90.6	30.9	6.2	158
52	0.34	13.4	91.9	30.9	6.1	236
53	0.26	12.1	95.6	32	6.5	218
54	0.99	NA	NA	NA	NA	NA
55	0.28	15	90.9	31.7	11.5	240
56	0.2	15.4	92	31.6	6.5	359
57	0.22	15.6	97.5	34.1	5.9	270
58	0.29	13	90.1	30.7	5.6	192
59	0.52	15.8	93.4	32.2	7.6	333
60	7.73	14.8	86.9	30.3	2.2	192
61	0.22	13.4	93	31.5	11.8	504
62	0.31	13.5	93	33	4.97	292
63	0.12	15.1	90.9	33.2	10.12	288
64	0.37	14	86.3	29.6	5.95	199
65	0.49	12.8	94.2	30.3	2.3	215
66	0.62	11.1	79	23.9	2.52	194
67	0.14	16.3	84.9	29.3	9.23	339
68	0.36	13.3	69.4	24.4	5.8	239
69	0.41	14.9	96.2	33.3	9.91	295
70	0.34	16	91.3	33.7	1.31	NA
71	0.18	16.8	92.9	35.8	2.47	92
72	0.28	12.2	95.9	31.5	1.9	240
73	0.34	15.4	96.6	32.4	4.7	279
74	0.4	14.9	62.1	20.9	10.93	252
75	0.33	16.6	92	29.8	6.7	290
76	0.33	14.2	82.8	27.8	4.82	274
77	0.21	13	67.1	22.3	7.69	192

Serial no.	MMA 0.38	Hb	MCV	MCH	WBC	Plt
78	0.24	15.6	85.8	30.4	7.95	312
79	0.17	16.9	87.7	30.6	4.1	185
80	0.15	14.3	89.6	30	7.48	245
81	0.23	16.9	94.7	33	4.13	316
82	0.16	15.4	91	30.8	6.7	392
83	0.29	14.1	92.6	31	3.4	316
84	0.23	16.3	92.9	34	3.4	191
85	0.29	15.1	87.7	29.7	5.55	190
86	0.24	15.8	91.6	31.5	9.3	244
87	0.19	11.7	102.4	35.4	10.26	428
88	0.14	15.4	105.5	36.4	17.28	312
89	0.22	14.9	85.9	29	5.14	300
90	0.24	13.5	90.9	31.3	8.2	243
91	0.71	9.8	67.7	21	5.4	427
92	0.11	13.3	90.7	31.8	5.7	228
93	0.24	15.8	92.8	32	5.3	212
94	0.27	15.5	92.3	31	5.3	266
95	NA	12.9	96.4	33.6	3.8	311
96	na	14.2	104.8	31.7	3.8	191
97	na	12.7	94.2	33.4	7.3	464
98	0.3	14.5	95.2	32.6	6.5	353
99	0.17	16.4	92.1	33.4	6.4	246
100	0.13	13.4	87.9	29	6.22	207
101	0.22	12.3	91	31.1	7.68	313
102	0.18	13	99.5	32.8	6.76	361
103	0.17	16.6	92.7	32.1	11.5	289
104	0.32	9	71.4	22.4	5.07	164
105	0.11	12.8	84.8	29.1	3.55	198
106	0.12	14	87.1	29.2	3.8	218
107	0.81	14.1	89.8	30.6	7.7	343

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