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May 10, 2002

Russell Katz, M.D., Director
Division of Neuropharmacologic Drug Products
Federal Drug Administration

Re: IND #63384
Human Phase II Study
Safety and Efficiency of MDMA-Assisted Psychotherapy
in the Treatment of Chronic PTSD

Dear Dr. Katz:

I am writing to clarify treatment recommendations for hypertensive crises involving sympathomimetic drugs that, although extremely unlikely, might theoretically occur in the course of MDMA-assisted psychotherapy research.

I am a Diplomate of the American Board of Emergency Medicine and am Certified by the American Society of Addiction Medicine. I am the Addiction Medicine Consultant to the UCSF-Mount Zion Pain Management Center. I am Co-Chair of the Resources and Development Committee of the American Society of Addiction Medicine.

At several scientific conferences in the past, I had occasion to meet clinicians who used MDMA therapeutically in the years before it was scheduled. I have also treated a number of patients who used MDMA recreationally and I have periodically reviewed the literature on its effects, including its toxicity.

I support the conduct of FDA approved therapeutic research with MDMA and I hope that the FDA and Dr. Mithoefer find a successful modification of this proposal.

As noted in a recent comprehensive review published in Chest (Varon, J. and Marik, P., p. 217), in hypertensive crises involving sympathomimetic drugs, the blood pressure should be lowered over a time frame of 30-60 minutes. Only in acute aortic dissection is blood pressure reduction a goal to be achieved in the first 5-10 minutes.

Nitroprusside, or other immediate acting anti-hypertensive drugs, would not necessarily be the drugs of first choice in the setting of sympathomimetic drug induced hypertension, even if severe. Other parenteral drugs, including nicardipine and phentolamine, are among those recommended in this review (Varon, J. and Marik, P., p. 223).

Phentolamine is the only agent mentioned in the 2002 PDR as suggested for treatment of acute, severe hypertension that might follow overdose with either Dexedrine (p. 1513) or Adderall (p. 3232). The use of phentolamine is also recommended, with alternatives and adjunctive agents, for sympathomimetic poisoning by other authorities (Linden, C.H. and Burns, M.J., pp. 2615-2616, Harrison's Principles of Internal Medicine, 15th Edition).

Both entries in the PDR and the Harrison's citation recommend sedation as the initial pharmacologic strategy in this setting. If anti-hypertensive drug treatment were initiated, the drug of choice would likely be phentolamine or other non-immediate acting drug that are not generally monitored with an arterial line.

An additional comment would be that the nature of both the psychopharmacologic effects of MDMA as well as the PTSD population to be studied makes the proposed office, rather than hospital, setting somewhat more ideal: the office being safe and familiar as opposed to the hospital, which for many patients has been a site of apprehension and personal loss.

The presence of an immediately available, currently practicing, board certified emergency physician and an experienced emergency department nurse, neither of whom would have any other duties, in the adjacent room along with appropriate

emergency drugs and equipment would make the office setting at least essentially equivalent, and likely superior, from an emergency medicine point of view.

Sincerely,

Howard Kornfeld, M.D.

Varon, Joseph and Marik, Paul E., "Review: The Diagnosis and Management of Hypertensive Crises," Chest, 2000; 118:214-227.

Linden, Chrisopher H. and Burns, Michael J., "Poisoning and Drug Overdose," Harrison's Principles of Internal Medicine, 15th Edition, Braunwald, et.al., 2001, McGraw Hill, New York, pp. 2595-2616.

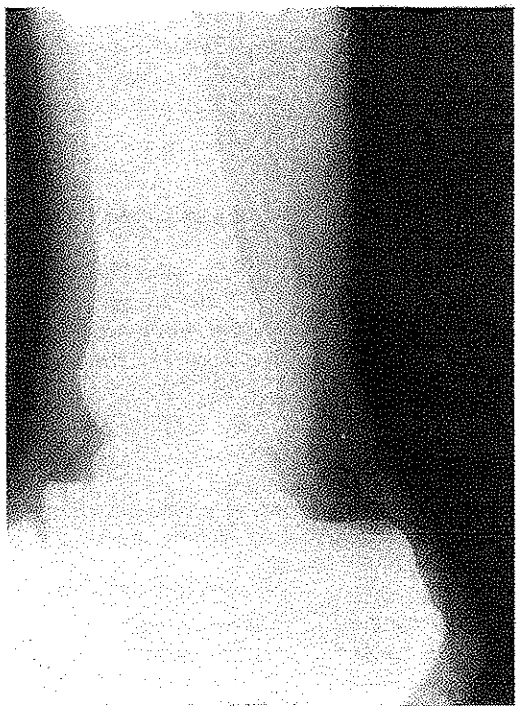

Fig. 2. Lateral ankle roentgenopraph in a patient suffering from a rupture of the Achiles tendon. Kager's triangle is small, less transparent, and covered by a network-like shadow. Toygar's angle has decreased and is less than 150°.

patients with acute total rupture, comparing with a reference groups of ankle fractures, ankle sprains and ankles without actual trauma. Kager's triangle was positive for rupture of the Achilles tendon in all patients, 12% had diminished Toygar's angle, 48% had positive Arner's sign, and 78% of patients with ruptured Achilles tendon had a thickness of the tendon compared with the opposite Achilles tendon. To lower the frequency of overlooked Achilles tendon rupture, any doubt as to whether a ruptured Achilles tendon is present should result in a lateral soft tissue roentgenographic examination of the ankle in all age groups. However, many radiographs of the ankle are taken to enable exclusion of fracture, and this does not always lead the physician to a correct diagnosis. The roentgenographic investigation should concentrate on Kager's triangle, which is easily identified and present a good specificity and a fine sensitivity for rupture of the Achilles tendon[8].

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REFERENCES

1. Michael S. & Banerjee A. (1993) Apparent tendo Achilles rupture in the elderly: is routine radiography necessary? *Archives of Emergency Medicine* **10**, 336–338.
2. Akermark C. (1992) Difficulty in diagnosing total rupture of the Achilles tendon. Every fifth case is missed by the physicians involved in the initial treatment. *Lakartidningen* **89**, 3681–3683.
3. Combalia A. (1994) Estudio estructural, ultraestructural y clínico de la rotura del tendon de Aquiles en el deportista. Tesis Universidad de Barcelona.
4. Józsa L., Kvist M., Balint B.J., Jarvinen M., Lehto M. & Barzo M. (1989) The role of recreational sport activity in Achilles tendon rupture. A clinical, pathoanatomical, and sociological study of 292 cases. *American Journal of Sports Medicine* **17**, 338–343.
5. Kager H. (1939) Zur klinik und diagnostik des achillessehnenrisses. *Chirurg* (Berlin) **11**, 691–695.
6. Toygar V.O. (1947) Subkutane ruptur der achillessehne, diagnostik und behandlungsergebnisse. *Helvetica Chirurgica Acta* **3**, 209–231.
7. Arner O., Lindholm A. & Lindvall N. (1958/59) Roentgen changes in subcutaneous rupture of the Achilles tendon. *Acta Chirurgica Scandinavica* **116**, 496–500.
8. Cetti R. & Andersen I. (1993) Roentgenographic diagnoses of ruptured achilles tendons. *Clinical Orthopaedics* **286**, 215–221.

Amphetamine, not MDMA, is associated with intracranial hemorrhage

A case report entitled 'Intracranial haemorrhage associated with ingestion of "Ecstasy"' is fraught with errors.[1] Chief among these errors are the misleading title and summary, as no 'Ecstasy' was involved. The authors define 'Ecstasy' as '3–4 methylene-dioxymethamphetamine (MDMA)', but go on to state that drug analysis revealed the presence of amphetamine, not MDMA. Consideration of MDMA as a possible aetiological agent was purely anecdotal, being derived from history given by a friend to the effect that the patient had 'apparently taken "Ecstasy"'. No information is presented from this friend as to the basis of her

belief — whether the patient had told her that she had ingested MDMA, whether she felt the patient's behaviour was consistent with 'Ecstasy' use, or for some other reason. While the patient's inability to speak at the time of admission explains why no history could be obtained from her at that time, her speech did return after treatment. Yet the patient's belief as to what she ingested is not reported.

Even documentation of the presence of amphetamine is inadequate: we are told that 'drug analysis detected...amphetamine at a concentration of 0.07 mg L^{-1}', but are not told whether this was the concentration of drug as sold in solution or in the patient's plasma, urine or some other bodily fluid.

Table 2, 'Management of "Ecstasy" overdose', is of potential interest but raises a number of questions. Is this protocol meant for treatment of MDMA overdose, amphetamine overdose, or both? Where did this protocol come from? Has this protocol been applied to the treatment of MDMA overdoshe? If yes, what was the outcome? The recommendation of phentolamine for the treatment of hypertension in amphetamine overdose is common, but other authors have noted that phentolamine has not been proven superior to sodium nitroprusside for this indication.[2] Continuous infusion of sodium nitroprusside permits more precise control of blood pressure than does bolus administration of phentolamine, and deserves consideration in the treatment of acute hypertension.

The report presented is both misleading and of unclear intent. If the point is to highlight the dangers of adulteration of illicit drugs then the title should reflect this and the inclusion of an MDMA overdose management protocol is of questionable relevance. Conversely, if the intent is to address the management of MDMA overdose, the inclusion of a case involving amphetamine is inappropriate. Certainly aldulteration of illicit drugs presents a variety of hazards and the MDMA-associated deaths at British rave parties were tragic and alarming. However, these points cannot justify deficient history taking or inaccurately titled reports.

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REFERENCES

1. Hughes J.C., McCabe M. & Evans R.J. (1993) Intracranial haemorrhage associated with ingestion of 'Ecstasy'. *Archives of Emergency Medicine* **10**, 372-374.
2. Ellenhorn M.J. & Barceloux, D.G. (1988) *Medical Toxicology: Diagnosis and Treatment of Human Poisoning.* Elsevier, New York.

Intracranial haemorrhage associated with ingestion of 'Ecstasy'? A response[1]

We apologize for the omission of a question mark at the end of the title which would have avoided any confusion. The aim of this short report was to warn practitioners of the increasing adulteration of illicit drugs in the UK, the inherent dangers for diagnostic error and the need to rely on formal drug analysis.

Patients presenting with a history of ingestion of 'ecstasy' is on the increase in the UK and therefore the management of 'ecstasy' overdose was included and based on the Welsh National Poisons Unit's Database.

The 0.07 mg L^{-1} refers to the level of amphetamine in the patient's plasma.

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REFERENCE

1. Hughes J.C., McCabe M. & Evans R.J. (1993) Intracranial haemorrhage associated with ingestion of 'Ecstasy'. *Archives of Emergency Medicine* **10**, 372–374.

Archives of Emergency Medicine, 1993, 10, 372–374

Intracranial haemorrhage associated with ingestion of 'Ecstasy'

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SUMMARY

A case of a patient with intracranial haemorrhage thought to have been associated with ingestion of 'Ecstasy' [3–4 methylenedioxymethamphetamine (MDMA)] is presented. The case illustrates the importance of drug analysis in cases involving illicit drug use.

CASE REPORT

A 21-year-old female presented to the accident and emergency (A&E) department. No history was available from the patient but a friend stated that she had apparently taken 'Ecstasy' a number of hours earlier. She later complained of headache, dizziness and paraesthesiae in her right arm and she was put to bed. There was no history of trauma.

The next morning she was incontinent and unable to speak. On admission to the A&E department she had signs of a complete right hemiparesis.

A CT head scan revealed a large intracerebral haemorrhage in the left fronto-parietal region, with significant mass effect, and surrounding oedema with shift of the midline (see Fig. 1).

She was given mannitol and dexamethasone before she underwent a left fronto-parasaggital craniotomy for removal of the intracerebral clot. At operation a small angioma was found which was felt to be the source of the haemorrhage. Drug analysis detected no MDMA but amphetamine at a concentration of 0.07 $mg\,l^{-1}$. Subsequently her speech returned but she has only partial recovery of power in her right arm and leg.

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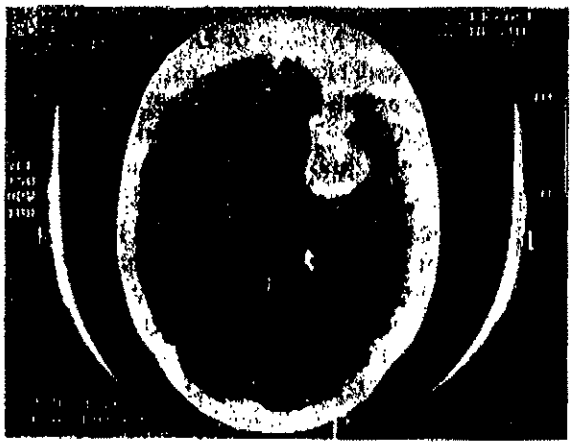

Fig. 1. CT scan showing large intracerebral haemorrhage in the left fronto-parietal region with significant mass effect and surrounding oedema with shift of the midline.

DISCUSSION

3,4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy', 'XTC', 'Love Doves', 'Dennis the Menace' or 'Adam' is a synthetic amphetamine derivative. The drug is taken orally as tablets or capsules in a dose of 50–150 mg.

The mechanism of toxicity is unclear but could be due to stimulation of peripheral and central alpha- and beta-adrenergic receptors. Severe reactions are unpredictable with early deaths most commonly resulting from cardiac arrhythmias and late ones (24–48 h post-ingestion) resulting from a syndrome resembling the neuroleptic malignant syndrome. Convulsions, collapse, hyper-pyrexia, disseminated intravascular coagulation, rhabdomyolysis and acute renal failure may occur. The long term effects are as yet unknown. Management is summarized in Table 1.

Intracranial haemorrhage is a recognized side effect of amphetamine ingestion (Gorelick, 1990; Kaku & Lowenstein, 1990), although not of its derivative 3-4 methylenedioxymethamphetamine.

Table 2. Management of 'Ecstasy' overdose

(1)	Supportive.
(2)	Oral activated charcoal (<4 h).
(3)	Monitor Pulse, B. P., temperature for at least 12 h.
(4)	Diazepam for anxiety/agitation.
(5)	Treat tachycardia with beta-blockers (e.g. atenolol).
(6)	Treat hypertension with Alpha-blockers (e.g. phentolamine).
(7)	Correct hypotension by volume expansion. Dopamine if necessary.
(8)	If rectal temperature >39°C, cool and administer dantrolene.
(9)	Monitor liver, renal, respiration, CPK and clotting.
(10)	Correct metabolic acidosis with sodium bicarbonate.

The recreational use of 'Ecstasy' in the U.K. has increased in recent years despite it being a Class A drug under the Misuse of Drugs Act 1971 and it is particularly associated with 'Raves' and 'Acid House' parties. A recent Harris Poll found that approximately 500 000 people are thought to have taken 'Ecstasy' on at least one occasion, with an estimated 20 000–30 000 people using it every weekend (Harris Poll, 1992). A recent survey of school children's knowledge of drugs showed an increase in their knowledge of 'Ecstasy' (Wright & Pearl, 1990).

While not free of complications (Dowling *et al.*, 1987; Chadwick *et al.*, 1991), 'Ecstasy' is generally thought by the public to be safer than amphetamines (Speed) (Henry, 1992). However, this case illustates that people may not be taking what they believe they are taking and therefore subjecting themselves to unexpected risks. A large proportion of illicit drugs may be mixtures of drugs other than that negotiated (Newcombe, 1992). It is worth taking this into account, when patients present with a history of drug ingestion of illicit drugs and rely on formal drug analysis.

ACKNOWLEDGMENTS

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REFERENCES

Chadwick I. S., Curry P. D., Linsley A., Freemont A. J. & Doran B. (1991) Ecstasy, 3–4 methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. *Journal of the Royal Society of Medicine* 84, 371.

Dowling G. P., McDonough E. T. & Bost R. O. (1987) 'Eve' and 'Ecstasy'. A report of five deaths associated with the use of MDEA and MDMA. *Journal of the American Medical Association* 257, 1615–1617.

Gorelick P. B. (1990) Stroke from alcohol and drug abuse. A current social peril. *Postgraduate Medicine* 88, 171–174, 177–178.

Harris Poll (1992) For the BBC Television programme 'Reportage' 22 January.

Henry J. A. (1992) Ecstasy and the dance of death (editorial). *British Medical Journal* 305, 5–6.

Kaku D. A. & Lowenstein D. H. (1990) Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Annals of Internal Medicine* 113, 821–827.

Newcombe R. (1992) A Researcher reports from the 'Rave'. *Druglink* Jan/Feb, 14–16.

Wrigth J. D. & Pearl L. (1990) Knowledge and experience of young people regarding drug abuse, 1969–89. *British Medical Journal* 300, 99–103.