Psychiatrische
Universitätsklinik Zürich

Ambulante, teilstationäre und stationäre Dienste

DR. F.X. VOLLENWEIDER, MD
Prof.Dr.med. Daniel Hell
Klinischer Direktor

Sektor Ost und zentrale Spezialangebote
Lenggstrasse 31
Postfach 68
8029 Zürich 8
Tel. 01-384 21 11
Fax 01-383 44 56

Dr. Russell Katz
Food and Drug Administration
Director, Neuropharmacological
Drug Products
5600 Fishers Lane
Rockville, MD
USA

September 14, 2001

Re: Human Phase II study – Safety and efficacy of MDMA-assisted psychotherapy in the treatment of chronic PTSD

Dear Doctor Katz,

I am the head of a 14-person psychiatric research team at the University of Zurich with extensive experience administering MDMA to MDMA-naïve experimental subjects. With the support from the Swiss Science Foundation and the Swiss Federal Office of Health, we have conducted over the last five years a series of placebo-controlled, double blind studies into the psychological and neurobiological effects of MDMA (1.5-1.7mg/kg) in more than 80 healthy human volunteers using positron emission tomography (PET), 3D-EEG, measures of sensorimotor gating, and neuropsychological measures. A list of our publications on our MDMA research is attached.

This letter is to offer my strong support for the proposed "Human Phase II study – Safety and efficacy of MDMA-assisted psychotherapy in the treatment of chronic PTSD" to be conducted by Dr. Michael Mithoefer and sponsored by MAPS. I have met with Dr. Doblin in Zurich and have carefully reviewed Dr. Mithoefer's protocol for this study. In sum, this is a careful and well designed study using state of the art methodology to evaluate the potential use of MDMA in treatment-resistant chronic PTSD patients who have failed to obtain relief from at least one full trial of an SSRI. The two doses of MDMA, each 125 mg., have been carefully chosen and should be of minimal risk when administered in a controlled clinical setting.

In our studies, we found no evidence that one or two doses of pure MDMA (e.g. 120-140 mg.) produce long-lasting neurological sequelae in humans. Moreover, a detailed retrospective analysis of our data obtained in MDMA subjects shows that one or two doses of MDMA produce no long-lasting effects on psychological and neuropsychological

measures, cerebral blood flow ($H_2{}^{15}O$-PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP).

Most importantly, preliminary analysis using PET and the radioligand McN-5256 revealed no significant changes in 5-HT transporter binding after a single dose of MDMA (1.5-1.7 mg/kg) was administered to 5 MDMA- naïve volunteers, evaluated with PET before their first MDMA session and again after 4 weeks (Vollenweider et al. 2000). We have a new PET paper in preparation based on research with several additional MDMA subjects (N=8) and a separate control group (N=6) receiving 3 PET scans after a placebo in order to more fully account for variations in the PET data. This expanded study confirmed our pilot study data showing no significant changes in 5-HT transporter binding after a single dose of MDMA (1.5-1.7 mg/kg). These findings support our initial assumption, based on a review of the existing literature, that such doses would not produce measurable neurotoxic effects.

The lack of measurable reductions in 5-HT transporter binding from doses of MDMA in the range of those to be administered in the protocol, combined with the absence of significant neuropsychological and other alterations, suggest that a rational risk-benefit analysis generates the conclusion that it is ethical to conduct the protocol as designed. As a result, I strongly recommend that this protocol be approved. If you have any questions about any of our studies, please feel free to contact me.

Dr. Franz X. Vollenweider, PD, M.D.
Head Behavioral Pharmacology and
PET program PUK Zurich

Reference List

Published Articles on MDMA by the University of Zurich research team, research conducted under the direction of Dr. Franz Vollenweider.

Vollenweider FX (1997) MDMA-Forschungen am Menschen: Strategien und erste Ergebnisse. SUCHT.Zeitschrift für Wissenschaft und Praxis 35-43

Gamma A, Vollenweider FX (1997) Ecstasy: regard médical sur cette drogue à la mode. Dépendance 4-5

Vollenweider FX, Gamma A, Liechti ME, Huber T (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") on MDMA-naive healthy volunteers. Neuropsychopharmacology 19: 241-251

Vollenweider FX, Remensberger S, Hell D, Geyer MA (1999) Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. Psychopharmacology 143: 365-372

Vollenweider FX, Gamma A, Liechti ME, Huber T (1999) Is a single dose MDMA harmless? Neuropsychopharmacology 21: 598-600

Gamma A, Buck A, Berthold T, Hell D, Vollenweider FX (2000) 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by ($H_2{}^{15}O$)-PET in healthy humans. Neuropsychopharmacology 23: 388-395

Liechti ME, Baumann C, Gamma A, Vollenweider FX (2000) Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology 22: 513-521

Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX (2000) Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT_2 antagonist ketanserin in healthy humans. Neuropsychopharmacology 23: 396-405

Liechti ME, Vollenweider FX (2000) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. J.Psychopharmacology 14: 269-274

Liechti ME, Vollenweider FX (2000) Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. Eur. Neuropsychopharmacology 10: 289-295

Vollenweider FX, Frei E, Gamma A (2000) Lokalisation MDMA-induzierter hirnelektrischer Aktivität bei gesunden Probanden mittels Low Resolution Brain Electromagnetic Tomoraphy (LORETA). In: Rihs-Middle M (ed) Suchtforschung des BAG. BAG, Bern, pp 5-11

Vollenweider-Scherpenhuyzen MFI, Vollenweider FX (2000) Emergency cases in drug abuse [Notfälle bei Drogenmissbrauch]. Der Internist 41: 886-898

Frei E, Gamma A, Pascual-Marqui RD, Lehmann D, Hell D, Vollenweider FX (2001) Localization of MDMA-Induced Brain Activity in Healthy Volunteers Using Low Resolution Brain Electromagnetic Tomography (LORETA). Human Brain Mapping 14: 152-165

Gamma A, Buck A, Berthold T, Vollenweider FX (2001) No difference in brain activation during cognitive performance between Ecstasy (MDMA) user and controls: A [$H_2{}^{15}O$]-PET study. J. Clin. Psychopharmacology 21: 66-71

Gamma A, Liechti ME, Vollenweider FX (2001) Giving MDMA to Human Volunteers in Switzerland. In: Holland J (ed) Ecstasy: The complete guide. A comprehensive look at the risks and benefits of MDMA. Park Street Press, Rochester, pp 327-337