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EDITORIAL

Caveat Emptor: Researcher Beware

These are strange and exciting times for researchers who work in the field of psychiatry. Technological advances and the ascendance of the new field of neuroscience, combined with our country's economic prosperity and consequent increases in the National Institutes of Health budget allocations, have created the potential for a virtual Golden Age of Biomedical Research. At the same time, psychiatric researchers are besieged by accusations from lay advocates and their organizations as well as inquiries by government agencies, including the Office of Protection from Research Risks (OPRR) and the National Bioethics Advisory Commission (NBAC) (1998). Among the most controversial issues have been studies employing high-risk designs, such as in pharmacologic challenge studies. Despite the fact that provocative testing is commonly used in medicine for both clinical and research purposes, this research design has evoked strong criticism particularly when used in psychiatric research.

The sensitivity of this issue is apparent in the letter by Gijsman and coworkers in this issue commenting on the article *Psychological and Cardiovascular Effects and Short Term Sequelae of MDMA ("Ecstasy") in MDMA-Näive Healthy Volunteers* by Vollenweider and coworkers (1998). The aim of this study was to extend studies of MDMA, a phenylethylamine of recreational use and abuse, by examining the effects of a single dose in healthy volunteers with no prior use of the substance. However, Gjisman et al. (p. 597, this issue) claim that "this study should not have been performed" because it "cannot be excluded that administration of a single dose of NMDA to humans causes damage to serotonin neurons." Vollenwieder and colleagues (1998) refute this criticism in their response (p. 598, this issue) and contend that there is no evidence indicating that single administrations at doses comparable to the 1.7 mg/kg administered in their study cause neurotoxic effects, and "reductions in 5-HT and 5-HIAA levels (which are produced by single doses) alone are not reliable indicators of neurodegeneration." At first glance, this might appear to be just another scientific difference of opinion. However, occurring in the current climate of public concern, this difference takes on greater significance. It may therefore be helpful to examine the issues that are inherent in this debate and of concern not just to Gjisman and colleagues (1999), but to the neuroscientific field and the public as well.

There are essentially three levels of concern about pharmacologic challenge studies in psychiatric disorders. The first involves the informed consent process and whether subjects are competent to provide it. This is a particular concern with psychiatric patients whose cognition might be impaired by their illness and who might therefore be more vulnerable. It is uniformly understood that informed consent is an essential requirement of all medical research and that participation of subjects must be wholly voluntary. Moreover, the subjects must understand the nature of the research and its potential for risks and benefits. The study in question used healthy volunteers who were screened for their histories of medical and mental illness. The authors state that the subjects were fully informed of previous toxicology study results with MDMA and provided written informed consent. The authors also indicate that the Ethics Committee of the investigators' hospital approved the study and the Swiss Federal Health Office Department of Pharmacology and Narcotics approved the use of MDMA. Thus, subjects appear to have been competent to provide informed consent and procedural standards appear to have been met.

The second level of concern involves risk that the procedure can cause harm to subjects. The notion of harm has been interpreted on two levels. At the first level, the question is whether the procedure can cause lasting biological or psychological injury, and at the second level, the question is whether it causes subjective distress to the subject. Generally, the former is of greater concern and is the point of criticism of the

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 21, NO. 4

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(99)00071-8

present study. The level of risk that is permissible in a study is a complex judgement involving the potential scientific and clinical gains that could potentially be obtained by the research and severity of the condition being studied. For example, the highly invasive controlled study of tissue grafts of adrenal or fetal tissue containing dopamine neurons in patients with advanced Parkinson's disease that involves sham surgery is justified by the dire nature of their condition, their unresponsiveness to other less invasive pharmacologic treatments, and the need to be certain that the treatment is effective (Olanow et al. 1997).

The study in question, however, was not a therapeutic study. Gjisman et al. (1999) contend that a single oral dose of MDMA seems likely to damage serotonin neurons in humans. The key study that the authors cite to support their point is that of Ricaurte et al. (1988), who reported that a single 5 mg/kg dose of MDMA produced long-term damage (assessed at two weeks) to the serotonin system in non-human primates. An examination of these data, however, indicate that while multiple oral doses of 5 mg/kg MDMA produced a large depletion of serotonin in all regions examined, a single oral dose produced no change in the frontal cortex, hippocampus, putamen, or caudate, and only a small change in the thalamus and hypothalamus. The absence of depletion in the frontal cortex and caudate is particularly important because these regions receive the type of fine fiber afferents from the dorsal raphe nucleus that have been shown to be most sensitive to MDMA neurotoxicity (O'Hearn et al. 1988; Wilson et al. 1989). Thus, it would appear that while Gjisman et al. (1999) raise valid concerns about this type of research in general and this study in particular, the data do not support the view that single oral doses at 1.7 mg/kg of MDMA (which was one third of the doses used in monkeys by Ricaurte et al. (1988)) are likely to produce damage to serotonin terminals.

As for the subjective experience of subjects administered the MDMA, it seems to have been on the whole pleasurable and it did not cause severe distress or any untoward behavioral reactions. A critical point that should be raised in connection with this is the potential for further abuse or addiction of subjects. In contrast to previous human studies, the subjects of Vollenweider et al. (1998) were nonabusers and naïve to the effects of MDMA. Thus, the question is whether this initial exposure places them at any risk for subsequent abuse. For this reason, it is imperative that this issue is described as a potential risk in the informed consent process.

The final level of concern is whether the quality and importance of the scientific information to be gained justifies the use of research designs that carry more than minimal risk and are viewed as controversial. Although any research in humans must be well designed and scientifically meritorious to justify putting any subject at risk, the level of potential scientific yield must be carefully scrutinized and meet a higher standard in studies involving greater than minimal risk, particularly those utilizing invasive procedures or placing subjects at risk, whether it be through drug free conditions or symptom provocation. Moreover, it has been suggested that nontherapeutic studies that involve greater than minimal risk should not be carried out in patients with decision making impairment (NBAC 1999). It should, therefore, be noted that the study by Vollenweider and colleagues (1998) was not of patients but healthy volunteers. It is important to emphasize that this level of critical analysis must be performed by all investigators in the design of clinical research and by IRBs in its evaluation.

These issues were the subjects of a recent Workshop on Pharmacologic Challenge Studies convened by the NIMH (1998). Among the conclusions reached was that such study designs are valid and ethical provided that two conditions are met: 1) there must be sufficient and clear scientific merit to the study in the form of testable hypotheses that will provide new knowledge; and 2) the risks must be minimized and justified in terms of the potential scientific gains. To ensure that these standards are applied and the relevant stakeholders are in agreement on these, the NIMH has established a Human Subjects Research Workgroup to review studies involving human subjects that may, reasonably, be expected to increase symptoms or distress including pharmacologic challenge studies that are being considered for finding by the NIMH. The workgroup will be a subcommittee of the National Advisory Mental Health Council. The hope is that the additional awareness and scrutiny of studies such as that employed by Vollenwieder et al. (1998) will ensure their safe and appropriate conduct, and reassure colleagues and observers like Gjisman et al. (1999).

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