The Consequences of 3,4-Methylenedioxyamphetamine Induced CYP2D6 Inhibition in Humans

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Abstract: 3,4-Methylenedioxyamphetamine (MDMA, ecstasy) is a widely abused substituted amphetamine. MDMA is predominantly O-demethylated in humans by cytochrome P450 isoforms 2D6 and 1A2 (CYP2D6 and CYP CYP1A2, respectively). MDMA is also a mechanism-based inhibitor of CYP2D6. A controlled clinical trial was conducted in 15 healthy male subjects whereby a probe drug, dextromethorphan (DEX), was administered after an oral dose of 1.5 mg/kg MDMA. The pharmacokinetics of DEX and its metabolites were used to evaluate changes in CYP2D6 activity. The urinary metabolic ratio of DEX and dextrorphan was used to calculate a recovery half-life of CYP2D6. After MDMA, DEX Cmax and area under the curve increased approximately 10-fold with corresponding decreases in dextrorphan pharmacokinetic parameters. The metabolic ratio increased almost 100-fold from 0.0061 ± 0.0056 to 0.4322 ± 0.2848 after MDMA administration, with 67% of the subjects having a value greater than the antimode of 0.3 for assigning the poor metabolizer phenotype. CYP2D6 activity recovered after 10 days with a recovery half-life of 46.6 hours. In addition to the possible long-term serotonergic effects of MDMA, users must be warned of the consequences of such an inhibition.

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paroxetine, also a potent mechanism-based inhibitor of the enzyme. Subsequently, Venkatakrishnan et al\textsuperscript{15} corrected this value for the elimination half-life of paroxetine (18 hours)\textsuperscript{16} to 51 hours. However, in deconvolving the values of the enzyme and the inhibitor, assumptions were made regarding the linearity of the relationship between the inactivator concentration and the extent of inactivation. Prediction from a model of in vivo MDMA kinetics indicates that it could take up to 260 hours for 90% recovery of the activity of CYP2D6 after a typical recreational dose.\textsuperscript{17}

The implications of the MBI of CYP2D6 by MDMA are different with respect to acute and chronic toxicity. Because this phenomenon is rapid and complete shortly after a single recreational dose, any genetic differences in the expression of the enzyme are minimized with respect to their role in susceptibility to acute toxicity, whereas the role of metabolism by other cytochrome P450 enzymes and renal excretion assumes greater importance with regard to systemic exposure to unchanged drug.\textsuperscript{18}

Given the implications of potent MBI of CYP2D6 by MDMA, we have attempted to assess the duration of this inactivation and hence the half-life of CYP2D6 by following the return of enzyme activity after single recreational doses using the urinary ratio of DEX/DOR as a biomarker. Approximately 90% of an oral dose of DEX is O-demethylated to DOR by CYP2D6, and the urinary metabolic ratio (MR) is used widely to assess the extent of the activity of the enzyme in vivo.\textsuperscript{14,19,20}

In addition, many methylenedioxy compounds have been observed to induce CYP1A2 in vitro.\textsuperscript{21} With this in mind and taking into account the involvement of CYP1A2 in the metabolism of MDMA, plasma concentrations of caffeine and its metabolite, paraxanthine, were monitored to mark CYP1A2 activity\textsuperscript{22} after a recreational dose of MDMA.

MATERIALS AND METHODS

Subjects

The study was conducted in accordance with the Declaration of Helsinki (2000), approved by the local institutional review board (CEIC-IMAS), and authorized by the Spanish Medicines Agency (AEM n. 04–0013) of the Spanish Ministry of Health. All subjects gave their written informed consent before inclusion in the study and were compensated for their participation.

Subjects were recruited by word of mouth. Eligibility required the self-reported recreational use of MDMA on at least 5 occasions and twice in the previous year. Each subject was interviewed by a physician to exclude concomitant medical conditions and underwent a general physical examination, routine laboratory tests, urinalysis, and 12-lead electrocardiogram. Subjects were interviewed by a psychiatrist (Psychiatric Research Interview for Substance and Mental Disorders for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) to exclude those with a history of or actual major psychiatric disorders (schizophrenia, psychosis, and major affective disorder).\textsuperscript{23} Fifteen individuals fulfilled the inclusion criteria and had a mean age of 26 years (range, 19–33), a mean body weight of 69.6 kg (range, 54.2–91.2), and a mean height of 181 cm (range, 171–196). Subjects reported an average of 26 previous experiences (range, 6–100) with MDMA. All but 4 were current smokers. None met the criteria of abuse or drug dependence (except for nicotine dependence). All had previous experience with other psychostimulants, cannabis or hallucinogens. None had a history of adverse medical or psychiatric reactions after MDMA consumption. The subjects were phenotyped for CYP2D6 activity using DEX as a selective probe (EM phenotype was required for participation).\textsuperscript{19}

Samples of 1 mL whole blood were taken for DNA extraction and CYP2D6 genotyping (DrugMEt; JuriLab Ltd, Kuopio, Finland). The following genotypes corresponded to the following DEX/DOR MR CYP2D6*1/*1 (0.0030), *1/*2 (0.0065 ± 0.0072; n = 5), *1/*4 (0.0058; range, 0.0040–0.0076; n = 2), *2/*4 (0.0186), *1/*5 (0.0043), *1/*9 (0.0037), *1/*10 (0.0051), *9/*10 (0.0099), *1/*17 (0.0016), and *2/*41 (0.0020).

Drugs

Dextromethorphan tablets (Romilar; Roche Farma, SA, Madrid, Spain) and white, opaque, soft gelatin capsules containing 100 mg of caffeine anhydride were supplied by the Pharmacy of the Hospital del Mar, Barcelona, Spain. (R,S)-MDMA was supplied by the Spanish Ministry of Health and was prepared in white, opaque soft gelatin capsules by the pharmacy of the Hospital del Mar. All drugs were administered by the oral route.

Study Design

A pilot trial was first conducted in 3 individuals to determine the optimal dosing intervals for DEX. Subjects participated as outpatients in 2 sessions. Session 1 (control) was over 2 days, and session 2 (inhibition) was over 7 days, with a minimum of 3 days between each session. The design was open because the principle variables measured were objective (pharmacokinetics of DEX and metabolites, caffeine and metabolites, and MDMA). During the sessions, subjects’ cardiovascular and subjective effects were monitored for safety reasons (continuous electrocardiogram, blood pressure, heart rate, and temperature) according to methods previously published.\textsuperscript{24,25}

Each session began at 7:30 AM after an overnight fast. An indwelling catheter was inserted into a subcutaneous vein in the forearm of the nondominant arm to obtain blood samples. Thereafter, the subjects remained seated in a quiet room. Drug administration commenced at 8:30 AM. In session 1, 30 mg of DEX and 100 mg of caffeine were given at 0 hour. In session 2, a 1.5-mg/kg MDMA dose (minimum, 75 mg; maximum, 100 mg) was given at 0 hour followed by 100 mg caffeine at 4 hours and repeated 30 mg doses of DEX at 4, 24, 48, 72, 96, and 168 hours. The dose of MDMA was chosen to be in the range of the quantities reported for a single pill of ecstasy.\textsuperscript{26} A light meal was provided 6 hours after initial drug administration. Subjects were asked to urinate before the session commenced.
empty the bladder (prebasal), and subsequently urine was collected for 0 to 8 hours in session 1 after DEX administration and 0 to 4, 4 to 12, 24 to 32, 48 to 56, 96 to 104, and 168 to 176 hours in session 2 after MDMA administration. Urine pH was measured; the urine was then acidified and aliquots stored at −20°C pending analysis.

Blood samples (8 mL) were taken at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 25 hours after DEX and caffeine administration in session 1 and at 0, 0.5, 1, 2, 4, 4.5, 5, 6, 8, 10, 12, and 25 hours after MDMA administration in session 2. After centrifugation at 4°C, four 1-mL aliquots of plasma were stored at −20°C pending analysis. Tobacco smoking was permitted 6 hours after drug administration. Subjects were requested to refrain from consuming any drug of abuse 2 weeks before and throughout the duration of the study, and they were asked to follow a xanthine-free diet 48 hours up to the beginning of each session. Regular ingestion of medication in the month preceding the study was one of the criteria of exclusion of the trial. Single doses of symptomatic medication were accepted up to the week preceding the trial. At each session and before drug administration, urine samples were collected for assay for drugs of abuse (opiates, cocaine metabolite, amphetamine, methamphetamine, and cannabinoids) by a rapid test device (Instant-View; Alpha Scientific Designs, Inc, Poway, Calif).

Dextromethorphan dosing intervals were changed after the observance that the urine MR had not fully recovered to basal levels after 168 hours. Hence, in the final phase, 12 remaining subjects entered the study with exactly the same design except that DEX was administered in session 2 at 4, 24, 72, 96, 168, and 240 hours with urine collection at 0 to 4, 4 to 12, 24 to 32, 96 to 104, 168 to 176, and 240 to 248 hours. Due to no major differences in DEX clearance and recovery of CYP2D6 inhibition between the pilot and the final phase, the results are presented together. Furthermore, caffeine and paraxanthine pharmacokinetics were not affected by previous administration of MDMA; hence, the results discussed herein will pertain to those concerning changes in DEX and metabolite pharmacokinetics as a measure of CYP2 activity.

### Assays Methods

Aliquots of urine and plasma were assayed for DEX, DOR, 3-methoxymorphinan (MM), and 3-hydroxymorphinan (HM) by means of high-performance liquid chromatography using a method previously described. The interassay precision and accuracy of urine assays were 11.4% and 10.1%, respectively, for DEX and 9.1% and 8.5%, respectively, for DOR, with limits of detection of 13 and 7 ng/mL, respectively. Corresponding values for the plasma assays were 14.6% and 12.3% for DEX, 12.0% and 9.5% for DOR.

### Table 1. DEX and Metabolite Pharmacokinetics Before (Session 1) and After (Session 2) a 1.5-mg/kg Dose of MDMA (n = 15; SDs in Parentheses; Values Calculated Using the Limits of Detection of the Assay)

<table>
<thead>
<tr>
<th>Session</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</th>
<th>t&lt;sub&gt;max&lt;/sub&gt;, h&lt;sup&gt;*&lt;/sup&gt;</th>
<th>AUC (8 h), ng/mL&lt;sup&gt;−1&lt;/sup&gt; × h&lt;sup&gt;−1&lt;/sup&gt;</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt;, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEX</td>
<td>1 3.5 (3.6)</td>
<td>6.0 (0.9)</td>
<td>15.7 (5.2)</td>
<td>1.7 (0.1)</td>
</tr>
<tr>
<td></td>
<td>2 29.7 (18.5)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6.0 (1.6)</td>
<td>149.1 (75.6)</td>
<td>9.0 (5.6)</td>
</tr>
<tr>
<td>DOR</td>
<td>1 464.6 (182.6)</td>
<td>6.0 (0.7)</td>
<td>1877.1 (676.2)</td>
<td>2.5 (0.6)</td>
</tr>
<tr>
<td></td>
<td>2 31.9 (12.6)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6.0 (0.8)</td>
<td>179.1 (77.6)</td>
<td>10.9 (5.7)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>MM</td>
<td>1 2.7 (2.0)</td>
<td>6.5 (2.1)</td>
<td>16.8 (5.3)</td>
<td>4.2 (2.0)</td>
</tr>
<tr>
<td></td>
<td>2 6.3 (5.1)</td>
<td>7.0 (2.2)</td>
<td>28.8 (24.2)</td>
<td>10.2 (12.3)</td>
</tr>
<tr>
<td>HM</td>
<td>1 164.1 (58.0)</td>
<td>6.0 (1.0)</td>
<td>764.2 (232.2)</td>
<td>3.5 (1.0)</td>
</tr>
<tr>
<td></td>
<td>2 16.6 (5.8)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8.0 (0.0)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>97.5 (38.0)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>37.3 (72.3)</td>
</tr>
</tbody>
</table>

<sup>*</sup>t<sub>max</sub> values are given as medians.

<sup>†</sup>AUC values in session 1 refer to 0 to 8 hours and in session 2 refer to 4 to 12 hours.

<sup>‡</sup>p < 0.05 by paired Student t test.

<sup>‡</sup>p = 0.008 by the Wilcoxon exact test for nonparametric values.
of MDMA was measured by the method of Pizarro et al. \cite{19}

\begin{align*}
\text{log transformed DEX/DOR urinary MR before (control) and after (inhibition) (n = 15; error bars = SE).}
\end{align*}

15.0% and 12.6% for MM, and 10.2% and 11.8% for HM, with limits of detection of 1.5, 2.5, 1.5, and 4.0 ng/mL for DEX, DOR, MM, and HM, respectively. Assay showed 100% selectivity for all compounds in both matrices as compared against 10 blank samples from distinct sources. Plasma MDMA was measured by the method of Pizarro et al. \cite{18}

**Data Analysis**

Values of the maximum plasma concentration (\(C_{\text{max}}\)) and the time to reach \(C_{\text{max}}\) (\(t_{\text{max}}\)) were noted directly from the plasma concentration-time profiles of DEX, DOR, MM, and HM. Area under the curve values (AUC [0,\(t\)]) were determined from 0 to 8 hours (session 1 data) and from 4 to 12 hours (session 2 data) using the trapezoidal rule. Elimination rate constants (\(k\)) were estimated by log-linear regression of terminal data points. Values of pharmacokinetic parameters were compared between sessions by the paired Student \(t\) test (\(C_{\text{max}}\) and AUC) and the Wilcoxon test (\(t_{\text{max}}\)). Differences were considered to be significant at \(P < 0.05\).

Relationships between urinary DEX/DOR MR and \(C_{\text{max}}\), MR and urine pH, and MR and urine creatinine concentration were assessed by the Pearson correlation coefficient. The fold change in MR values at the mean of each urine sample period in session 2 relative to the MR value in session 1 \(A(t)\) was plotted against time after MDMA dosage for each volunteer. A monoexponential equation was fitted to the individual profiles by nonlinear regression, with weighting by the SD of the MR in the respective urine sampling interval to estimate a value of CYP2D6 recovery half-life (ln(2)/\(K_{\text{cyp}}\)).

\begin{align*}
A(t) = A(0)e^{-K_{\text{cyp}}t} \tag{1}
\end{align*}

where \(A(t)\) is the fold change in DEX urinary MR after MDMA administration expressed by \(\frac{MR_{\text{inh}}}{MR_{\text{control}}}\) at the midpoint of time interval \(t\), \(A(0)\) is the baseline value, and \(K_{\text{cyp}}\) is the first-order rate constant for CYP2D6 recovery. Goodness of fit of each equation to the observed values was evaluated by visual examination of residual and observed versus predicted plots.

**RESULTS**

**Plasma Concentrations of DEX, DOR, MM, HM, and MDMA Pharmacokinetics and Pharmacodynamic Effects**

The plasma concentrations of DEX and DOR before and after a 1.5-mg/kg dose of MDMA are shown in Figure 1. \(C_{\text{max}}, t_{\text{max}},\) and pharmacokinetic values for DEX, DOR, MM, and HM are summarized in Table 1. After MDMA, DEX \(C_{\text{max}}\) and AUC (8 hours) increased approximately 10-fold with a similar decrease in corresponding values for DOR and HM. Plasma concentrations of MM were not changed by MDMA. The mean \(C_{\text{max}}\) of MDMA was 194.3 ± 30.9 ng/mL with a \(t_{\text{max}}\) of 2.0 ± 1.0 hours, AUC\(_{0-25}\) of 1939.7 ± 484.7 mg/mL h\(^{-1}\), and mean residence time (1/\(K_{\text{e}}\)) of 13.3 ± 2.3 hours. The administration of a single dose of 1.5 mg/kg MDMA produced the typical effects described for this substance in an experimental laboratory setting (increases in blood pressure and heart rate, mydriasis, feelings of well-being, and euphoria). No adverse effects were noted after MDMA administration.

**Urinary DEX/DOR MR and CYP2D6 Recovery Half-Life**

The MR increased almost 100-fold from 0.0061 ± 0.0056 (session 1) to 0.4322 ± 0.2848 (session 2), with 67% of the subjects having a value greater after MDMA administration than the antimode of 0.3 for assigning the PM phenotype.\(^{19}\) A significant correlation was observed between MR and \(C_{\text{max}}\) (DEX)/\(C_{\text{max}}\) (DOR) (\(r = 0.594; P = 0.002\)). A correlation was not detected between MR and urine pH (\(r = 0.049; P = 0.863\)) nor between MR and urinary creatinine concentration (\(r = 0.214; P = 0.395;\) session 1). The time course of recovery of the CYP2D6 activity represented by log (MR) after MDMA dosage is shown in Figure 2. The monoexponential equation generated predicted values that correlated well with the fold change observed \((r^2 = 0.791)\), and a plot of the residuals against time interval showed was randomly scattered. The estimated value of \(K_{\text{cyp}}\) was 0.016 ± 0.005 hours, giving a CYP2D6 recovery half-life of 46.6 ± 11.8 hours.

**DISCUSSION**

A single recreational dose of MDMA caused a dramatic increase in the systemic exposure to the model CYP2D6 substrate DEX, with a concomitant decrease in exposure to its primary metabolite DOR. This was also reflected in a marked change in the urinary DEX/DOR MR, which had not recovered fully to its basal level at 10 days after MDMA dosage. These observations, which seem to reflect potent MBI of CYP2D6, confirm implications suggested by previous investigations.\(^{17}\) Thus, there is rapid phenocopying to apparent PM status after a single dose of MDMA, explaining the inability to relate acute toxicity with...
CYP2D6 genotype.\textsuperscript{29} In addition, there are implications for potent and prolonged inhibition of the metabolism of other CYP2D6 substrates that might be taken after a single dose of MDMA (including SSRIs, other amphetamines, and DEX itself, which is also subject to abuse\textsuperscript{30}) and for understanding of the determinants of MDMA kinetics on continuous dose.\textsuperscript{17} Similar findings have been reported with paroxetine, also a potent mechanism-based inhibitor of CYP2D6 with comparable $k_I$ and $k_{deg}$ values in vitro.\textsuperscript{31,32} However, the in vivo effect of paroxetine was less marked, with no phenocopying to PM status.\textsuperscript{14} This difference may reflect differences in dose (20 mg paroxetine vs 1.5 mg/kg MDMA [75–100 mg]) and systemic exposure to the 2 drugs.

In this study, we used the DEX/DOR urinary MR as an index of CYP2D6 activity. It is clear from the results that the variability of the MR is large and as such merits explanation. This MR is sensitive to any changes in the renal clearance of DEX, for example, due to urine pH-dependent excretion.\textsuperscript{33,34} However, we did not detect any material influence of urinary pH or renal function as measured by urine creatinine on the DEX/DOR MR. Nevertheless, because the volunteers in this study were from a homogeneous sample and their dietary intake was not significantly variable, differences in renal function and pH values were not significant enough to allow observation of these effects within the small sample size.

The mean value of CYP2D6 half-life of 46.6 hours that we have estimated is less than the value of 70 hours previously estimated using paroxetine as an inhibitor.\textsuperscript{14} Although this may reflect differences in the subjects studied, our value is within the 95% confidence interval of that reported previously. However, it is similar to that calculated by an in vitro-in vivo extrapolation model.\textsuperscript{15} Venkatakrishnan et al\textsuperscript{15} assumed that the unbound paroxetine plasma concentrations were less than its $K_I$, and hence the CYP2D6 $K_{deg}$ was obtained by deconvolving the enzyme turnover rate and inhibitor elimination rate constant. In the present study, plasma concentrations reached a maximum of 194.3 ± 30.9 ng/mL, and assuming that unbound plasma concentrations of MDMA are less than or equal to concentrations of MDMA at the active site of CYP2D6 and are below its $K_I$ value (5.8 μM),\textsuperscript{35} the MDMA mean residence time ($1/K_I$) can be subtracted from the CYP2D6 mean residence time ($1/K_{seg}$) to obtain a corrected half-life value of 37.4 ± 11.6 hours. This value underestimates even further the time of recovery seen here. Conversely, observing the data in Figure 2 and assuming that CYP2D6 recovers 90% of full activity within 3 to 4 half-lives, this value seems to underestimate the recovery because CYP2D6 activity has not recovered fully even after 10 days. Due to these problems of underestimation and because the data, after log transformation, seem to recover following a biphasic model, we attempted to fit a biphasic exponential equation to the results. A biphasic model can be explained by differences between CYP2D6 turnover rates in the gut and liver or a dominant competitive inhibitory component in the first days after MDMA administration with MBI being more apparent in the following days. The latter model gives a CYP2D6 half-life of 103.0 ± 70.3 hours, and on deconvolving MDMA MRT, a corrected half-life of 93.7 ± 70.4 hours is calculated. However, it should be stated that the variability in the data and the lack of sufficient data points over time question the validity of the biphasic model.

The dose of 1.5 mg/kg was chosen here to mimic a single recreational dose of MDMA.\textsuperscript{26} It has been shown that a dose greater than 50 mg would almost completely inactivate CYP2D6 in the liver, with a dose of 100 mg almost completely inactivating CYP2D6 for up to 24 hours.\textsuperscript{17} Indeed, we have shown in a previous in vivo study that the concentrations of MDMA are significantly increased even when the second dose is taken 24 hours later beyond what is expected from accumulation of concentration.\textsuperscript{12} Furthermore, MDMA users are known to on average take more than 1 pill per session, with doses averaging from 1.8 to 2.9 pills per session reaching a maximum of 6 to 7 pills depending on the type of user.\textsuperscript{36} It has also been documented that many users “binge” on ecstasy, and these binges may last several days.\textsuperscript{37} Users must be warned that the risk of acute toxicity due to these practices is drastically increased. Evidence presented here suggests that a second dose of MDMA taken up to 1 week later would present higher plasma concentrations and higher risk of acute toxicity. It can even be suggested that MDMA users who use the drug on a frequent basis have a permanently compromised CYP2D6 activity.

In this investigation, one of the most relevant CYP2D6 mechanism-based inhibitors marked for possible toxic drug interactions is the SSRI antidepressant, paroxetine. Differences in doses taken and the way in which the drugs are administered have repercussions for their respective toxicities. Paroxetine for instance is a well-studied, prescribed commercial drug, and continuing medical education in psychiatry has increased awareness by prescribers of the potential for drug-drug interactions.\textsuperscript{38} 3,4-Methylenedioxymethamphetamine is an illegal substance taken at higher but inexact doses outside the scope of medical supervision. A single recreational dose of MDMA rapidly and completely inhibits CYP2D6, whereas several prescription doses of paroxetine are needed to achieve a similar inhibition.\textsuperscript{34,39}

It is known that MDMA users are not exclusive users of the drug and belong to a poly-drug abusing population. Dextromethorphan itself is abused at much higher doses than those given in this study,\textsuperscript{40} and its abuse in combination with MDMA would cause a toxic interaction. Any other substituted amphetamine that is a CYP2D6 substrate would also potentially interact with MDMA in this manner. Other possible interactions would be with the SSRI previously mentioned or other substrates of CYP2D6 such as codeine, tramadol, risperidone, and metoprolol among others. However, the only fatal interaction reported to date has been with the antiretroviral and CYP3A4 substrate ritonavir.\textsuperscript{40} On a pharmacodynamic level, SSRIs such as citalopram and paroxetine block the positive effects of MDMA.\textsuperscript{41,42} Indeed it has been suggested that MDMA users may take common SSRIs to modify the effects of MDMA.\textsuperscript{43} It should be noted, however, that although the neuropharmacodynamic effects of the drug would be changed, individuals using SSRIs in conjunction with multiple doses of MDMA must be made aware that the metabolism of both substances is compromised leading to possible increase of the risk of acute adverse effects already reported for CYP2D6 poor metabolizers.\textsuperscript{44}
Furthermore, it has been found that many ecstasy users present some sort of psychopathologic problem. Some of these individuals may seek treatment and could be prescribed an SSRI. Health care providers must be made aware of the dangers of prescribing such medication to such a population.

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AUTHOR DISCLOSURE INFORMATION
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