Appendix I: Workshop Summary Outcome Measures and Success Criteria

Betty Tai

On October 8, 1992, the second Clinical Decision Network workshop sponsored by the Medications Development Division (MDD), National Institute on Drug Abuse (NIDA) was held in Bethesda, Maryland. There were 30 attendees at this workshop (see attachment I). The agenda of this workshop addressed specific issues regarding standardized outcome measures and definitions of success of clinical efficacy trials for cocaine addiction pharmacotherapy. These two issues were identified in an earlier workshop (held April 20-21, 1992) as missing elements in current research and development processes for cocaine addiction pharmacotherapy. The meeting program was divided into two parts. The morning session included brief presentations by invited participants, which provided introduction, overview, background, and objectives of the workshops. Two workshops were conducted during the afternoon session, with participants divided into small groups. Discussions were focused on specific issues regarding using biological markers, e.g., urine, to assess cocaine use (workshop I), and defining abstinence as an outcome measure (workshop II) in conducting clinical efficacy trials.

Workshop I - “Assessment of Drug Use” group 1 was moderated by Richard Hawks and Paul Fudala; group 2 was moderated by Nora Chiang and Reese Jones. Workshop II, “Definition of Abstinence” group 1 was moderated by Peter Bridge and Jeff Wilkins; group 2 was moderated by Frank Vocci and Jim Cornish.

EFFICACY OUTCOME MEASURES

Participants generally agreed that the outcome measures for assessing the clinical efficacy of cocaine addiction pharmacotherapy should reliably and accurately reflect the benefits of the treatment. A core battery of outcome measures has been proposed by Dr. Charles O'Brien's group. Participants unanimously agreed that urinalysis should be used as an efficacy outcome measure. The advantage of this is obvious, as this is the best of the currently available surrogate markers for monitoring cocaine intake. However, this method has its

limitations; therefore, it is important to thoroughly understand the basic pharmacokinetics concepts and analytical methods applied to the urine screening of cocaine exposure to ensure proper experimental design and data analysis. Participants also expressed the desire to have some standardized method of collecting, analyzing, and interpreting urinalysis data so that results may be readily compared across studies.

USE OF URINE DATA TO ASSESS COCAINE USE BEHAVIOR

Urinalysis of cocaine, benzoylecgonine (BE), or other metabolites is a surrogate measure for cocaine exposure. To use urine data reliably and accurately to estimate actual cocaine use, it is important to fully understand the underlying principles and the current state-of-the-art technology for urinalysis.

Pertinent Issues

Some of the following issues (the pharmacokinetics of cocaine and the clinical relevance of urinalysis in measuring drug use) were discussed in the workshop, some (the chemical analysis, the sampling scheme of the urine samples, and the trial designs) were not. For the purpose of having a complete record as a general background for later discussion, the author has supplemented some of the information.

Pharmacokinetics. Cocaine, whether administered intranasally or intravenously, has a fast onset of action coupled with a speedy rise of plasma cocaine concentration. The bioavailability via the intranasal (IN) route is about 50 to 80 percent and via the smoke route is about 10 to 20 percent. Cocaine has short half-life of about 1.5 hours. BE and ecgonine methyl ester, the major nonactive metabolites of cocaine, have half-lives of 7.5 and 3.5 hours, respectively. Therefore, BE is the most commonly screened target and can be detected in the urine for up to 2 days after the last cocaine use. Depending on the frequency of urine sampling and the pattern of cocaine use (daily use versus binge use), a negative urine sample may not be a clear indication of lack of cocaine use, and a positive urine sample may be due to the carried-over effects of a previous episode 3 to 5 days before sampling.

Chemistry. Both immunoassay and chromatography methods have been used to detect urine BE. Immunoassays such as EMIT, RIA, and

Abbott ADX have been popular for qualitative measurements because they are less expensive, have fast turnaround, and are reliable. Generally, 300 ng/mL is set as the cutoff. Results are expressed as positive or negative on the basis of BE concentrations. Recently, some laboratories have been using GC or GC/MS for quantitative assays of BE concentrations in urine. This raises new possibilities for analysis and interpretation of urine data. Extensive discussion on this implication was part of the workshop agenda. Different methods have different sensitivity, specificity, and reproducibility of detection. Therefore, it may be advantageous to have a central laboratory analyze all the samples collected from multisite trials. This becomes critical when considering whether quantitative urine measures would be useful in particular studies.

Trial Design (Statistics). Although it was not the focus of discussion at this workshop, design and statistical issues are unavoidable in meaningful discussions about using urinalysis to monitor cocaine intake. Major relevant issues are the design of sampling schemes (random or fixed schedule) used to collect samples, the frequency and timing of sampling, and quantitative versus qualitative analysis of urine data. These issues are critical in designing trials that would minimize the carryover effect and maximize the possibility of detecting cocaine intake. The issue of how to treat missing samples is critical in analyzing urinalysis data. Conservative methods usually count a missing sample as a positive sample. However, justification for such statistical treatment is needed. One strategy is to shorten the trial duration to minimize the missing datapoints.

Clinical Relevance. From the above discussions it is clear that there are limitations in using urinalysis data to estimate cocaine use behavior. Generally, urinalysis data are not very sensitive markers because of high variability. It is extremely difficult to use urine data to estimate the frequency and amount of cocaine use. Changes observed in urinalysis data have not been correlated with changes in any other outcome variables such as patients' well-being, employment status, or marital status. Until such correlations are established, the clinical usefulness of urine data is limited to validating reported drug use.

Urine Data Analysis: Qualitative Versus Quantitative

The current urine analysis methods were developed for detecting illicit drug use in the workplace. For cocaine detection, the urine concentration of BE (a major inactive metabolite with longer half-life)

is analyzed by immunoassays. A BE concentration of 300 ng/mL was set as the cutoff point. Any sample with a concentration below 300 ng/mL is a negative sample (a clean urine), any sample with a BE concentration above 300 ng/mL is a positive sample (a dirty urine). This is the qualitative method of cocaine detection, which only provides information on whether a cocaine metabolite is present in the urine sample. Lately, several laboratories have been applying chromatography assays and a fluorescence polarization immunoassay to determine actual urine BE concentrations. Therefore, instead of binary assessments of urine samples as either clean or dirty, it is possibile to evaluate urine data in a continuous, quantitative manner. However, the quantitative urinalysis is more time consuming and costly. The advantages and the limitations of the quantitative urinalysis to project cocaine intake behavior were therefore extensively discussed. There was general consensus that it holds significant promise for use in outcome measures of some trials, but that it may offer limited (or no) advantage in others. Clearly more research is needed to resolve the value of the quantitative approach versus the qualitative approach.

Urine Data Interpretation

Reduction in Use. Traditionally, the treatment goal for addiction disorder is to achieve total abstinence. The idea of accepting reduction in use of abused substance as an interim goal for treatment was new and novel to many workshop participants. However, it was felt that because the outcome for treatment for any group of patients is a continuum, measuring improvement by a reduction in the amount of illicit drug use was not unreasonable. Similar to that for many other incurable diseases, the treatment objective may be to bring symptoms into remission. Fewer episodes of use, or reduction in amount of illicit drug use, certainly is an encouraging sign for treatment success. Treatment success may also be viewed as phases or stages: initially, reduction in use may be the goal; ultimately, reduced use leads to availability for other treatments that leads to abstinence.

Reduction in use means reduced amount or/and frequency of cocaine intake. The latter has a significant implication for intravenous (IV) cocaine users, because this would reduce the risk for HIV exposure and conversion. However, some of the participants pointed out that the validity of the assumption that reduction in cocaine use will lead to abstinence or improved scores on the other Addiction Severity Index (ASI) measures and/or prevent the deterioration due to cocaine addiction has not been established through long-term treatment

studies. There was a legitimate difference of opinion as to the prognostic significance of minor reductions in cocaine use, although all participants agreed that major reduction in cocaine use was a good prognostic sign.

With qualitative urinalysis, reduction in use may be expressed collectively in decreased numbers (or percentages) of positive (dirty) samples or increased numbers (or percentages) of negative (clean) samples within a specified study period, and individually as decreased or increased number of days of urine samples being positive or negative. However, in a recent report by Batki and Jones on the effect of fluoxetine on cocaine use, the authors' results showed that with qualitative urinalysis a statistically significant difference was not achieved between the treatment and control, whereas a statistically significant difference was achieved with quantitative urinalysis. This report sparked extensive discussion on how quantitative urinalysis could provide additional information or improve the sensitivity of urine data in assessing cocaine use behavior.

In quantitative urinalysis, if a significant decrease of mean urine BE quantity between the treatment and placebo groups is observed, the following issues need to be addressed: (1) Is the spread (variability) of the data wide or narrow? The data may reflect only a few heavy users who changed their use behavior. (2) Are subjects stratified by their preferred route of cocaine administration? The bioavailability of the smoking route is much lower than those of the IN and IV routes of cocaine administration. (3) Does an X percent decrease in mean urine BE concentration indicate a parallel X percent reduction in the amount of cocaine intake? If not, what is the correlation between the urine data and amount of cocaine use? (4) Should this reduction be interpreted as X percent of the population achieved a certain level reduction of cocaine intake or that everybody in the study reduced the use by X percent? At present, the demonstration of a reduction of mean urine BE quantity is collective information, i.e., it does not reveal the nature of the reduction. Until these issues are addressed, quantitative urinalysis will be more effective in projecting cocaine use only when it is backed up with additional evidence of efficacy.

Participants generally felt that because of the insensitivity of the biological marker as an outcome measure, any statistically significant reduction in the biological marker measure must project a much more pronounced reduction at the behavior level. Participants also suggested that the acceptable reduction criteria must be set at the behavior level rather than at the urine level. In designing the trial, it is

important to set a target for reduction, so that the N (number of study subjects) that will give maximal power may be determined.

Abstinence. Participants generally agreed on the definition of abstinence as continuously drug-free days; abstinence can be expressed by urinalysis data as continuous clean days. Note that because of intermittent sampling and possible carryover, clean urine days rather than abstinent days are measured. In other words, days of negative urine do not equal days of abstinence. Urinalysis data can only demonstrate clean urine days and cannot tell the difference between a slip and a relapse. A slip is considered a minor instance of use, but a relapse is a return to addiction. As relapse is not defined by the extent of use, but by symptoms of dependence, urinalysis data are therefore not helpful in differentiating the two. No participant was comfortable about judging relapse on the basis of urinalysis data.

Participants agreed that the proper duration for assessing abstinence depends on the addict's cocaine use pattern. For a daily cocaine user, 4 weeks of observation is considered sufficient. However, for a binger, the time for observation needs to be longer. Most participants considered the patient's being able to abstain for 50 percent of the trial duration a significant improvement. An occasional slip is not considered significant.

In summary, abstinence is not a terribly useful concept. The concept of relapse is important but cannot be evaluated with urinalysis data because relapse is defined by the dependence criterion. It is important to establish the baseline use pattern, i.e., daily user versus binge user. Many participants felt that for cocaine abuse, episodes of compulsive use is a more meaningful measure of efficacy than is abstinence.

Success Criteria. What kind and magnitude of reduction in use is considered clinically significant? Participants expressed the following opinions:

1. If a 10 percent reduction means everybody in the study reduced cocaine use by 10 percent, it is not significant, but if 1 out of 10 subjects stopped using cocaine, it is significant.

2. A reduction in use from seven to three injections per day is significant because it reduced the risk for HIV transmission.

3. A reduction in use from seven to five injections per day is not impressive, but a reduction from 7 to 5 days per week is impressive.

4. For a daily cocaine user, 1 abstinent day per week is significant. However, for a cocaine binger, days of abstinence do not mean much.

5. The timing of the reduction in use is also important in determining the significance; if the reduction in use occurred at the beginning of the trial and toward the end of the trial, the use pattern returned and the reduction cannot be viewed as effective.

CONCLUSION

While clear consensus on all the discussion points was an elusive goal, it was clear that much more thought is currently being given to more innovative ways to use urine data for outcome measures in clinical efficacy trials. Researchers are at the stage where new technology allows the generation of relatively quantitative results on urine samples, and such data hold interesting promise for identifying trends in drug efficacy. The many technical, clinical, and statistical issues raised in these discussions has laid critical groundwork for developing standardized approaches to the application of urinalysis for drug abuse pharmaco-therapeutics development. Having a marker that could accurately and reliably measure the episodes and amount of each cocaine intake would be ideal.

Unfortunately, current available technology and methods of urine screening do not provide such information. For effective use of urinalysis results as a surrogate outcome measure of the effect of pharmacotherapy on cocaine usage, the participants recommended the following:

1. Urinalysis is a useful objective outcome measure to monitor cocaine usage.

2. The sampling frequency should be appropriate to the objectives of the study; for cocaine, more than once weekly is needed.

3. A baseline measure of use pattern should be established with more than one urine sample and for longer than 1 week.

4. Urine data should be collected in a way that allows quantitative and qualitative analysis and is not dependent on a specific collection hypothesis or analytical plan.

5. The urine data should be investigated at specific points as well as over periods to see if there is a trend of reduction. If a trend is noted, what is the timecourse of the reduction? Is the reduction at the beginning or the end of the trial?

6. Self-reports, which provide information of timing, episodes, and amount of use, should be collected along with urine samples.

7. All urine data should be evaluated for the individual as well as the group, because there will be some who stopped use, some who reduced use, some who did not change. For those who have reduced or stopped use, other signs of improvement (employ-ment, marriage, etc.) should be examined to see if there is any correlation.

8. When submitted for Food and Drug Administration (FDA) review (according to Dr. Curtis Wright), the urine data should be collected, analyzed, and summarized in the most straightforward way possible. In some cases it may be advantageous to have the clinician evaluate the urine data while the trial is still blind, integrating the urine toxicology with the clinical reports. In other cases it may be best to keep the urine data confidential during the double-blind period. In either case, rules for collection procedures, attribution of missing samples, handling of dropouts, and the proposed analysis should be specified in advance.

ATTACHMENT I

Participant List

The participants of the workshop are listed below. Many of them have read and commented on this summary report. However, the choices of what to incorporate and how to present the materials are

those of the author, who, therefore, takes full responsibility for any errors.

Tanya Alim, M.D.
George Bigelow, Ph.D.
Jack Blain, M.D.
Peter Bridge, M.D.
Nora Chiang*, Ph.D.
James Cornish, M.D.
Everett Ellinwood, M.D.
Marian Fischman, Ph.D.
Paul Fudala, Ph.D.
Donald M. Gallant, M.D.
Charles Grudzinskas*, Ph.D.
Sue Herbert, M.A., R.N.
Richard Hawks*, Ph.D.
Reese Jones*, M.D.
Thomas Kosten, M.D.
Frances Levine, M.D.
Walter Ling, M.D.
Juri Mojsiak, D. Pharm.
Jack Mendelson, M.D.
Ann Montgomery, M.S., R.N.
Charles O'Brien, M.D., Ph.D.
Kenzie Preston, Ph.D.
Adel Roman, R.N.
Doralie Segal, M.S.
Charles Schuster, Ph.D.
Betty Tai, Ph.D.
Jeffery Wilkins, M.D.
George Woody, M.D.
Curtis Wright*, M.D., M.P.H.
Frank Vocci*, Ph.D.

* = Participants who have read and commented on the summary report.

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