PREFACE

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More than 23 million Americans have used cocaine at some time in their lives, and more than 1.3 million are current cocaine users. Cocaine abuse and dependence affect all segments of society with devastating personal, social, and public health consequences. Unfortunately, effective cocaine pharmacotherapies are lacking. Accordingly, the National Institute on Drug Abuse (NIDA) has made the development of an anticocaine medication its number one priority.

More than 30 marketed medications have been tested in the last decade for their effectiveness to treat cocaine addiction. Several review articles (see Elinore F. McCance's chapter, this volume) were published and general conclusions are: (1) most of the open trials had positive results; however, when the studies were repeated in a blinded manner, the results became negative, which leaves the development potential of these medications unclear; (2) the clinical research efforts were primarily focused on the evaluation of a broad range of the marketed medications in the absence of reliable animal and/or clinical models to predict clinical utility; and (3) the heterogeneity across study design coupled with the lack of standardization of methodology used by the researchers in conducting these clinical studies made it impossible to evaluate and compare results for different studies to determine which medications should be advanced for further clinical evaluation.

One classical example of the lack of methodology standards can be illustrated with the review of studies of desipramine, a tricyclic antidepressant that has been widely prescribed to treat cocaine dependence (Halikas et al. 1991). More than a dozen clinical studies have been conducted and published since 1982. A meta-analysis of the published trials was attempted (Levine and Lehman 1991). This task proved to be extremely difficult because of the heterogeneity in the design of the various studies. Some of the subjects who were studied were primarily cocaine abusers, some were methadone maintained, and others were dually diagnosed. The inclusion/exclusion criteria were very different for each study. Regarding dose regimens, the more recent studies provided blood levels instead of doses. The protocol designs included random/nonrandom, open/blind, and controlled/uncontrolled study designs. In general, five categories of outcome measures have been commonly used: psychiatric outcome measures, craving, subjective drug effects, pattern of drug use, and retention in treatment. However, in these published studies, the definitions of outcome measures varied; the instruments and methods used in collecting the outcome measures varied; the questions asked, the adjectives used in forming these questions, and the scales used to assess the subjective effects varied; the sources and frequency for monitoring drug use patterns varied;

and the ways the data were analyzed and expressed also varied. These factors made it very difficult to interpret the study results and reach conclusions about whether desipramine is or is not efficacious in treating cocaine addiction.

In light of this, in 1992 the Medications Development Division (MDD) of NIDA proposed the establishment of a Clinical Decision Network, the objective of which was to create an alignment of opinion leaders in academia, government, and the pharmaceutical industry to address issues pertinent to conducting successful anticocaine clinical efficacy trials. The specific goals for this Network were to: (1) ensure that initial pharmacologic activity studies generated information that would be useful in predicting future clinical efficacy, (2) develop common outcome measures and consistent definitions of trial success so that comparison across studies could be made, and (3) create a Clinical Decision Tree to accelerate the development of treatment medications for cocaine addiction.

A series of workshops have been conducted since 1992 to identify and resolve the practical problems confronting researchers in conducting cocaine medication efficacy trials.

- MDD Workshop I (4/20/92)

  Identified the elements missing in the current clinical trial paradigm and Task Forces appointed. Summary was reported in the College on Problems of Drug Dependence (CPDD) (Tai 1992).

- MDD Workshop II (10/18/92)

  Reviewed Task Force Proposals on outcome measures and success criteria. Summary report published by MDD. (See appendix I.)

- MDD Workshop III (11/13/92)

  Reviewed Task Force Proposals on Clinical Decision Tree. Summary report presented at CPDD in 1993. (See appendix II.)

Workshop results were summarized and disseminated at 1992 and 1993 CPDD annual meetings and at the 1992 American College of Clinical Pharmacology (ACCP) annual meeting. The culmination of the effort of these workshops resulted in a NIDA Technical Review meeting "Medications Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials," which was held in October 1994 at NIDA. The presentations at this Technical Review were arranged into three sessions. The first session provided an overview of the rationale for pharmacotherapeutical approaches and a comprehensive review of the compounds tested in the past 5 years. The second session targeted issues critical to the design, implementation, analysis, and interpretation of clinical efficacy trials for anticocaine addiction medications. The third and final session focused on a thorough investigation of the limitations and effectiveness of using qualitative and quantitative urinalysis, which is one of the core outcome measures to assess cocaine use in the clinical trials.

This monograph presents the proceedings of the October 1994 Technical Review. It is the editors' hope that this monograph will stimulate further research in the area of development and application of more sensitive clinical trial methodologies for drug abuse research, i.e.: (a) sensitive outcome measures (surrogate or direct) that effectively measure medical improvement in short treatment periods, (b) valid and reliable instruments to measure the above-mentioned outcome measures, (c) animal and/or human pharmacological models that are sensitive for predicting clinical relevance of testing compounds, (d) impact of interaction with levels of psychosocial support, and (e) the inclusion and exclusion criteria of subpatient populations with comorbidity and polysubstance abuse and how they affect the trial designs.

With sensitive methods and standardized processes, future trials may be compared meaningfully and allow valid, critical development decisions to be made to accelerate the identification, evaluation, and development of anticocaine addiction medications.

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