

Appendix II: Workshop Summary Clinical Decision Tree for Cocaine Addiction Pharmacotherapy

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A coherent research and development (R&D) plan to effectively and efficiently move compounds into multicenter efficacy trials for cocaine addiction pharmacotherapy does not exist at present. In light of this, in 1992, the Medications Development Division (MDD) of the National Institute of Drug Abuse (NIDA) sponsored three Clinical Decision Network workshops to identify, investigate, and develop actions that would facilitate the development of such a plan. From the first workshop, it was identified that the key missing element is the lack of a clinical decision tree that provided guidance in critical decision making regarding the selection, prioritizing, and discontinuation/ elimination of compounds from R&D process. In subsequent workshops (held on November 13, 1992) proposals were reviewed to address these issues, and a clinical decision tree (see figure 1) was developed with the following key features: (1) an assumption that the investigational compounds are with or without a strong clinical pharmacology model (table 1); (2) if the compound has a strong clinical pharmacology model, then development rationale, in initial safety, pharmacokinetics, and interaction with abused substances may be tested in human laboratory settings (table 2), if not other proper hypothesis-generating trials; and (3) for all compounds, the efficacy confirmation trials may be tested with designs specific to the proposed indication (table 3).

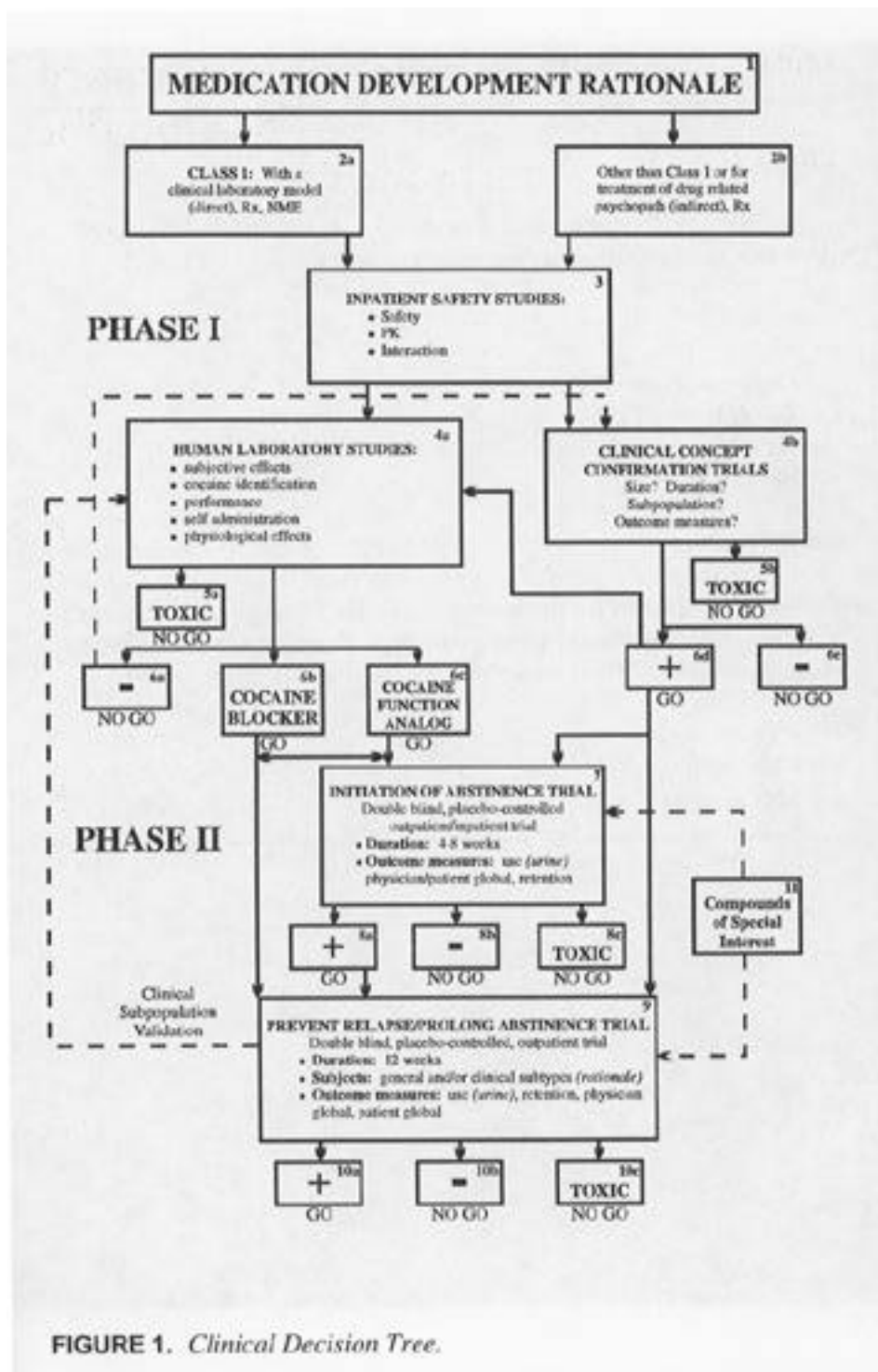


FIGURE 1. Clinical Decision Tree.

TABLE 1. *Characteristics of compounds.*

Class 1

With a clinical laboratory testing model (e.g., substitute/replace, block cocaine transporter, monoamine receptors, etc.)

Sources

- Drug discovery
- Champion
- Rx experience
- Special class

Class 2

Other than Class 1 or for the treatment of underlying psychopathology (e.g., reverse/normalize neuropharmacologic function or treat specific clinical problems associated with cocaine abuse/dependence, etc.)

- Rx experience
 - Champion
 - Special class
-

TABLE 2. *Phase I: Human laboratory studies.*

OBJECTIVES	Safety dose range Activity dose response Interaction of cocaine and testing compound
SUBJECTS	General cocaine-experienced volunteers
DURATION	1 day to 2 weeks
SETTING	Laboratory
OUTCOME	(Cocaine alone, cocaine + test medication)
MEASURES	Safety: CV, behavior, mood Subjective effects: ARCI, POMS, VASS, liking/craving Drug stimulus Self-administration: Free access, choice

Adapted/modified from abuse liability testing.

TABLE 3. *Phase II: Clinical efficacy/safety studies.*

OBJECTIVES	Indication specific <ul style="list-style-type: none">• Efficacy for initiating abstinence• Efficacy for relapse prevention or prolonging abstinence
SUBJECTS	Cocaine dependents stratified by: <ul style="list-style-type: none">• Severity• Use pattern• Comorbidity
DESIGN	Randomized control trial (RCT)
DURATION	1. 4 to 6 weeks 2. 8 to 12 weeks
SETTINGS	Inpatient or outpatient
OUTCOME MEASURES	Safety: CV, behavior, physiologic state, serum chemistry, etc. Efficacy: Drug use - self-report, biologic markers Retention in treatment Patient self-assessment Physician assessment

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