

5-2003

Single Versus Multiple Drug Focus in Substance Abuse Clinical Trials Research

Nancy M. Petry

University of Connecticut School of Medicine and Dentistry

Follow this and additional works at: https://opencommons.uconn.edu/uchcres_articles

 Part of the [Medicine and Health Sciences Commons](#), and the [Social and Behavioral Sciences Commons](#)

Recommended Citation

Petry, Nancy M., "Single Versus Multiple Drug Focus in Substance Abuse Clinical Trials Research" (2003). *UCHC Articles - Research*. 176.

https://opencommons.uconn.edu/uchcres_articles/176



Published in final edited form as:

Drug Alcohol Depend. 2003 May 21; 70(2): 117–125.

Single versus multiple drug focus in substance abuse clinical trials research

Bruce J. Rounsaville^{a,b,*}, Nancy M. Petry^c, and Kathleen M. Carroll^{a,b}

^aDepartment of Psychiatry, Division of Substance Abuse, Yale University, West Haven, CT 06516, USA

^bVA Connecticut Healthcare (151D), New England Mental Illness Research Education and Clinical Center, 950 Campbell Avenue, West Haven, CT 06516, USA

^cDepartment of Psychiatry, University of Connecticut Health Center, Farmington, CT 06030, USA

Abstract

Complex patterns of multiple substance use pose clinical and methodological challenges for substance abuse clinical trials research. To increase measurement precision and internal validity, the modal approach has been to target both treatment interventions and outcome assessment to a single class of abused substance. This strategy warrants reconsideration because it entails limitations in recruitment feasibility and generalization of study findings. This report reviews pros and cons of single versus multiple targeted drugs, suggests guidelines for choosing between these strategies and outlines methods for broadening the scope of substance abuse clinical trials to take abuse of multiple substances into account. We recommend that investigators consider moving away from a single drug focus in three ways. First, include systematic assessment of a wide range of psychoactive substance use throughout the trial and evaluate the impact of study treatments on use of all classes of drugs. Second, except where contraindicated, include patients who use and abuse multiple classes of substances even in trials evaluating treatment of a single targeted drug. Third, consider inclusion of polysubstance abusers or those who primarily abuse multiple classes of substances in the same clinical trial. Although many treatment efficacy questions can best be answered by single focus studies, we recommend that such designs be adopted only after less restrictive designs are first considered.

Keywords

Treatment; Clinical trials; Pharmacotherapy; Polysubstance abuse; Methodology; Technology transfer

1. Introduction

Calls to ‘bridge the gap’ (Institute of Medicine, 1998) between clinical research and clinical practice have highlighted the need to consider how a new treatment will fare in community settings at all stages of treatment development and efficacy testing (Rounsaville et al., 2001). Choosing study patients who are representative of those likely to be seen in community settings can facilitate ultimate dissemination of experimental treatments (Hohmann and Shear, 2002). In designing and implementing treatments, both community

clinicians and academic researchers must contend with considerable heterogeneity in choice of abused substances across patients and within patients over time.

One major gap between community and research treatments results from differences in the ways that clinicians and researchers respond to patients' complex patterns of substance use. Clinicians must take patients as they present themselves and attempt to manage the full range of a patient's clinically significant substance abuse. Stimulant, sedative, and opioid dependent patients may all be treated within the same clinic and context. Abstinence from all substances is almost exclusively the goal in most community-based treatment settings. In contrast, the modal approach for pharmacotherapy or behavioral therapy efficacy research has been to target a single abused substance. Patients with current dependence on other substances or multiple substances are often excluded from efficacy trials. Ratings of use of the targeted drug are often considered the primary outcome measure, with other drug use addressed in only a tangential or cursory fashion.

In the service of narrowing this particular gap between clinical practice and clinical research, this report will re-evaluate strategies related to focusing on just a single type of drug use. After reviewing pros and cons of single versus multiple targeted drugs, we will suggest guidelines for choosing between these strategies. We will also outline methods for broadening the scope of substance abuse clinical trials to take abuse of multiple substances into account.

2. Why focus on the principal abused substance?

Focusing substance abuse efficacy research on a single targeted substance makes clinical and methodological sense because pharmacological actions, natural history and assessment issues vary widely across different abused drugs. We will briefly review the clinical and research implications of these cross-drug differences.

2.1. Pharmacological specificity

The specific pharmacological actions of different classes of drugs provide a strong rationale for a single drug focus in some types of clinical trials. Studies that evaluate new medications for substance abuse, in particular, are likely to benefit from focusing upon a single drug of abuse. Most fundamentally, the rationale for using medications for substance abuse is based on the treating agent's mimicking, altering or blocking some aspects of the abused drug's specific pharmacological effects. Medications typically are effective for treating one class of abused drugs, such as disulfiram for alcohol dependence or methadone for opioid dependence. Therefore, most pharmacotherapy trials focus on just a single drug of abuse.

Safety issues are more complex and difficult to estimate when many types of substance abusers are included within a pharmacotherapy trial. Interactions between a treatment agent and more than one abused substance may become quite complex. For example, it is clearly necessary to exclude current opioid users in trials evaluating opioid antagonists for alcohol dependence. Another drug-specific set of safety issues arises from variations in the need for pharmacologically assisted detoxification prior to initiation of experimental treatments, as drugs like heroin and sedatives are associated with medically significant withdrawal syndromes while cocaine and marijuana are not.

Pharmacological specificity poses fewer challenges pertaining to rationale and safety issues when examining behavioral treatments. Hypothesized actions of behavioral treatments (e.g. enhancing motivation, learning new coping strategies) are usually applicable across different classes of substance abuse and many major types of behavioral therapies have been demonstrated to be effective across different classes of substance types (Carroll, 2001).

Safety issues are also less pressing in examining behavioral therapies, as long as patients in need of pharmacologically assisted detoxification are excluded or managed clinically prior to onset of study treatment.

2.2. Common natural history and standard treatments

Targeting a single drug of abuse avoids clinical and methodological challenges arising from differences across substances in the populations affected, age of onset, course, adverse consequences and standard treatment. These features can have a major impact on prognosis, intensity of treatment and requirements for services in addition to those included in research protocols. In particular, patients who use legal versus illicit substances and those dependent on opioids versus other illicit substances may be particularly difficult to treat in a single treatment protocol. The prognostic significance of client characteristics associated with use of legal versus illicit substances (e.g. educational level, employment status, legal system involvement) may exceed the power of the experimental intervention to influence treatment outcomes.

Treating outpatients dependent on heroin and on other substances in the same treatment protocol is especially problematic because of the widespread use and high impact of agonist (e.g. methadone) maintenance for heroin abusers. For ambulatory heroin patients, offering experimental treatments outside of a methadone program risks unacceptably high attrition. Conversely, the powerful impact of methadone maintenance on treatment retention and reduction of opioid use works against including such patients in clinical trials of treatments for ambulatory cocaine abusers for whom effective medications are not available (Warner et al., 1997).

2.3. Common assessments

Targeting a single drug of abuse avoids assessment challenges arising from differences across substances in dosage, routes of administration, pharmacokinetics and pharmacodynamics. Biological measures of substance use are particularly sensitive to variability in absorption and elimination half-life across abused substances, with extremes defined by rapidly metabolized agents like nicotine and long lasting drugs like cannabinoids. To verify abstinence, these differences translate into very different requirements regarding the type, frequency and expense of biological testing to be employed (see Schwartz, 1988). Testing for a full range of substances must err on the side of either excessive assessment for long lasting substances or inadequate assessment for short lived ones.

Cross-drug measurement issues are not confined to biological measures. Validity of self-report is highest when independent of consequences (e.g. Babor et al., 2000; Del Boca and Noll, 2000), and it is likely to vary across legal and illicit substances (e.g. Lu et al., 2001). Moreover, because of cross-substance differences in amounts and patterns of use, standards for measuring clinically significant improvement tend to vary by substances. The distinction made by alcohol researchers (e.g. O'Malley et al., 1992) between a 'slip' and a 'relapse' may be meaningful for a legal drug for which quantities can be accurately reported but much less meaningful among illicit substances for which quantity can only be guessed. Similarly, the distinction between 'drinking days' and 'heavy drinking days' (Babor et al., 1994; Project Match Research Group, 1997) or gender-related differences in 'safe drinking guidelines' (Sanchez et al., 1995) may be meaningful for some treatments for alcohol dependence, but these distinctions are far less commonly used in treatment outcomes of illicit drug use disorders (Rohsenow et al., 2000).

Focus on a single substance also can maximize the sensitivity of outcome assessment. During the course of a treatment intervention, a significant percentage of patients may be

able to maintain abstinence from, or substantially reduce use of, one primary or targeted substance. A principal aim of complete abstinence from all psychoactive substances, on the other hand, may be applicable as both a quantifiable result and a clinical outcome. However, such a measure is insensitive due to the comparatively low rates of total abstinence achieved in most clinical trials of substance abuse treatments (e.g. Crits-Christoph et al., 1999). Moreover, the heterogeneity of drug use patterns among substance abusers, and the frequently observed pattern of greater baseline drug use being associated with poorer outcomes (e.g. McLellan et al., 1994), may obviate potentially statistically significant and clinically meaningful reductions in drug use if such a stringent outcome criterion of complete abstinence is applied.

3. Drawbacks to a single drug focus

Although these issues noted above argue for focusing on a single drug target, equally compelling reasons can be considered for including patients with a broader range of drug use diagnoses in clinical research trials. Above all, when studies focus on a single abused substance, generalization, feasibility, and efficiency are compromised.

3.1. Unrepresentative subject group

Substance abusing patients who exclusively abuse a single substance have become progressively scarce and unrepresentative of the general population of substance abusers in community and clinical settings. Both population and clinical surveys (Ball and Ross, 1991; Caetano and Weisner, 1995; Helzer and Pryzbeck, 1988; Martin et al., 1996; Tsuang et al., 1994; Regier et al., 1990) indicate that the majority of those with a current substance use disorder use multiple psychoactive substances and meet current or lifetime criteria for a number of substance use disorders. For example, estimates indicate that 30–60% of alcohol-dependent individuals abuse cocaine (Caetano and Weisner, 1995; Martin et al., 1996; Tsuang et al., 1994), 20–50% abuse marijuana (Caetano and Weisner, 1995; Martin et al., 1996; Tsuang et al., 1994), 12–20% abuse benzodiazepines (Ciraulo et al., 1988; Ross, 1993) and 7–10% abuse heroin (Caetano and Weisner, 1995; Martin et al., 1996; Tsuang et al., 1994). Prevalence of marijuana abuse in cocaine-dependent patients ranges from 25 to 70% (Higgins et al., 1994; Hubbard, 1990; Schmitz et al., 1991), and lifetime prevalence of alcohol dependence exceeds 65% in both treatment-seeking cocaine users as well as those not seeking treatment (Carroll et al., 1993). Fifty, 33, 47 and 69% of heroin-dependent patients are regular users of alcohol, benzodiazepines, cocaine, and marijuana, respectively (Ball and Ross, 1991). Cigarette smoking is also common, with up to 63–90% of treatment-seeking substance abusers reporting daily nicotine use (Budney et al., 1993; Burling and Ziff, 1988; Cunningham-Williams et al., 2000).

3.2. Compromised feasibility

Thus, abuse of multiple substances is the rule and not the exception. Recruiting a sample of 'pure' substance abusers poses feasibility issues, as only a small subset of clinical or community abusers will meet this criterion. Moreover, even if a sample can be recruited, singly dependent patients are likely to be unrepresentative of the general population of drug abusers in ways that limit generalization of findings.

3.3. Limited generalization of safety and efficacy findings

For pharmacotherapies, failure to study a heterogeneous population leaves safety and efficacy issues unanswered. A new drug may have toxic or other interactions with non-targeted abused substances. Examining the effects of pharmacotherapies on multiple classes of drugs may also reveal unexpected beneficial effects, as medications may reduce use of drugs other than the targeted one via direct or indirect mechanisms. For example, methadone

maintenance treatment is associated with not just reductions in opioid use, but decreases in other drug use, such as cocaine and benzodiazepines, as well (Ball and Ross, 1991). Naltrexone can be used for treating both opioid (Greenstein et al., 1997) and alcohol (O'Malley et al., 1992; Volpicelli et al., 1992) dependence. Disulfiram has shown some efficacy in reducing alcohol use (Fuller et al., 1986; Chick et al., 1992), as well as cocaine use (Carroll et al., 1993, 2000; Petrakis et al., 2000; George et al., 2000). Although the mechanisms of action may differ across the drug classes, the beneficial effects could only be discerned by including polysubstance abusers in the trials and evaluating the effects of these medications on use of multiple substances.

3.4. Potential bias of efficacy results

Moreover, samples of 'pure' abusers are likely to have a narrower range of drug-related consequences. They may be more amenable to treatment, thereby inflating estimates of the treatment's efficacy (Hughes et al., 2000). Thus, in the process of development and efficacy testing of treatments (Rounsaville et al., 2001), focus on a single drug may be inefficient and lead to premature conclusions about a treatment's promise, for both pharmacological and behavioral treatments.

3.5. Inefficiency of behavioral therapies development

Behavioral treatments typically target psychological processes common to abusers of many different substances such as conditioned craving or poor self-efficacy. When new behavioral techniques are developed, focus on a single abused substance can be inefficient because initial positive findings would require replication on abusers of a succession of other, individual substances. Such repeated testing has been conducted on the use of motivational enhancement therapy for the treatment of nicotine, alcohol, and cocaine dependence (e.g. Dunn et al., 2001), and the use of cognitive-behavioral strategies for nicotine, alcohol and other drug dependences (Carroll, 1996). On the other hand, failure of initial studies with an arbitrarily chosen patient sample may lead to premature abandonment of a treatment with promise for abusers of another class of drugs.

Hence, initial pilot testing of new behavioral treatments should utilize a heterogeneous patient sample unless the treatment is targeted to processes underlying a specific type of substance abuse, or a particular group of substance abusers who are likely to share a common psychosocial problem. For example, designing a therapy that addresses unemployment among methadone patients may reasonably exclude non-opioid dependent patients, as unemployment rates may be much lower in other samples, or attrition rates may be higher among non-methadone maintained substance abusers.

In contrast, initial testing of pharmacotherapies generally should usually target a single drug of abuse because the rationale for medication treatments is nearly always based on the actions of a specific class of abused substances. Subsequent studies may examine their efficacy and safety in more heterogeneous samples who have both the target drug use diagnosis, as well as additional substance use problems.

3.6. Limitations in some common strategies

To increase feasibility of recruitment and generalizability of results, many clinical trials incorporate strategies to broaden the eligible subject pool beyond those who exclusively abuse a single substance. These strategies include (a) selecting subjects according to the 'primary' or 'principal' drug of abuse, (b) allowing concurrent use or abuse but not dependence on substances other than the targeted drug and/or (c) allowing other types of substance abuse (e.g. nicotine, marijuana) to go unmonitored or ignored in treatment interventions or outcome evaluation. Each of these approaches involves limitations. For

example, selecting subjects by principal drug of abuse excludes potential subjects who cannot choose among a number of heavily used drugs or who use drug combinations preferentially (e.g. 'speed-ballers' who use a combination of heroin and cocaine). More importantly, ignoring other types of drug use in monitoring or outcome assessment may miss potential hazards or benefits of the study treatment pertaining to non-targeted substances. For example, a new treatment's beneficial impact on reducing use of the targeted substance may be counterbalanced by an increase in other substance use. Conversely, attention to a wide range of substance outcomes can reveal unexpected applications for the experimental treatment. For example, O'Malley's interest in naltrexone's potential as a treatment for nicotine dependence (Krishnan-Sarin et al., 1999) was generated by increased naltrexone side effects in alcohol dependent subjects who were cigarette smokers. Smokers who took naltrexone first thing in the morning prior to smoking a cigarette were especially susceptible to intense nausea. This connection between nicotine abstinence and greater naltrexone side effects suggested a link between nicotine and endogenous opioid activity. Follow up research confirmed this hypothesis (Krishnan-Sarin et al., 1999) and suggested a potential role for opioid antagonists in treating nicotine dependence. As a further example, a study of contingency management interventions found reductions in illicit drug use occurred when alcohol abstinence alone was reinforced in alcohol-dependent patients (Petry et al., 2000).

In a series of clinical trials evaluating behavioral and pharmacological treatments of cocaine dependence, our group has used the approach described in the previous paragraph by selecting patients whose self-identified principal abused drug is cocaine while allowing for current abuse but not dependence on a range of other substances. This strategy has yielded subject populations that appear representative of cocaine abusers in general clinical samples (Carroll et al., 2000) but a limitation of this work is our lack of measurement or analysis of several classes of concurrently used substances, most notably nicotine.

4. Broadening the scope of substance abuse clinical trials: factors favoring focus on one versus multiple substances

4.1. Three recommendations

To maximize the scientific yield of substance abuse clinical trials research and to facilitate ultimate community use of empirically validated treatments (Rounsaville et al., 2001), we recommend that investigators move away from a single drug focus in three ways. First, include systematic assessment of a wide range of psychoactive substance use throughout the trial and evaluate the impact of study treatments on use of all classes of drugs as part of routine testing for efficacy and safety. Second, except where contraindicated (see Section 4.2), include patients who use and abuse multiple classes of substances even in trials evaluating treatments for a single targeted drug. Third, consider inclusion of patients who abuse or are dependent upon multiple or different classes of substances within the same clinical trial. The first two recommendations can be addressed in the majority of clinical trials while the third may have more restricted applicability.

4.2. Questions to guide the choice between single versus multiple drug focus

Given the previously reviewed factors favoring a single drug focus, single drug study designs clearly will not be abandoned. Rather, we recommend that such designs be adopted only after less restrictive designs are first considered. In deciding between a single or multiple drug focus (or the specific types of drug use to be excluded), investigators can attend to a number of questions. First, does the experimental treatment have a narrow or substance-specific hypothesized mechanism of action? As noted above, most pharmacological drug abuse treatments are hypothesized to affect a single class of abused

substances while behavioral treatments tend to target processes common to many types of substance abuse. Hence, inclusion criteria may need to be narrower in trials evaluating pharmacological versus behavioral treatments. Second, are there contraindications for use of the experimental treatment with use of non-targeted substances? These contraindications are most likely to apply to experimental pharmacological treatments and include such widely known combinations as naltrexone for active opioid users, disulfiram for alcohol users or MAO inhibitors for stimulant users. Third, is the targeted drug less addictive or associated with less severe consequences than the ancillary drug? For example, a trial targeting marijuana use or cigarette smoking may reasonably exclude patients currently dependent on opioids or cocaine, because dependence upon these latter substances may be more clinically significant than dependence on the former. A case could be made, nevertheless, to specifically examine the efficacy of smoking or alcohol cessation interventions in opioid dependent patients, so long as the patients are concurrently receiving acceptable standard treatment for their more clinically significant drug use diagnosis. Relatedly, does the intensity of standard treatment for the ancillary drug exceed that of the targeted substance? Again, the clearest exclusion of this type would involve exclusion of heroin dependent patients in trials targeting other substances, unless the study targets this particular type of polysubstance abuse. Fourth, do the demographic and clinical characteristics of the abusers of different substance abusers differ so greatly that separate clinical trials are warranted? While there can be no sharp distinctions regarding degree of acceptable heterogeneity, one might question the wisdom of, for example, including such disparate groups as retired, elderly alcoholics and court-mandated heroin addicts in the same behavioral interventions trial. Fifth, does the study design require use of biological markers (e.g. hormone levels) or other assessments that may be invalidated by use of multiple substances? Negative answers to these five questions would suggest the feasibility of including multiple types of substance abusers and poly-substance abusers in the same clinical trial.

5. Managing methodological challenges of heterogeneous samples

The increased external validity and recruitment feasibility of focusing on heterogeneous samples are obtained at the cost of (1) inclusion of multiple assessments, (2) challenges of devising common outcome measures across multiple types of drug abuse and (3) need to manage extraneous variability in the study design.

5.1. Dealing with assessment burden

Differences across drugs in mechanisms of action, use patterns and metabolism have generated a wide array of substance-specific biological and psychometric assessments. These differences are particularly important if biological assessments constitute the principal outcome measure as the frequency of assessment and the nature of the sample (e.g. serum, urine, saliva) varies widely across abused substances. To reduce study costs and excessive subject burden, investigators may restrict the range of assessed substances to those that can be measured with a single sampling procedure or re-conceptualize the biological assessments as validators of self-reported use. Generally, self-reported substance use remains the most commonly utilized outcome measure for clinical trials with acceptable reliability and validity, particularly when coupled with objective measures designed to verify self report (Babor et al., 1994, 2000; Carroll, 1995).

Many instruments with established reliability and validity permit assessment of quantity, frequency, or severity of multiple classes of substance use including the Timeline Followback Method (Sobell and Sobell, 1992), the Addiction Severity Index (Alterman et al., 2000; McLellan et al., 1985), the Substance Dependence Severity Scale (Miele et al., 2000), and the Severity of Dependence Scale (Gossop et al., 1995, 1997). Unfortunately, instruments for assessing dimensions of substance abuse other than quantity/frequency tend

to cover only a single class of substances. Hence, many widely-used assessments of craving (Anton and Drobos, 1998), drug-related expectancies (Galen and Henderson, 1999; Solomon and Annis, 1989), and motivation to change (Cunningham et al., 1997; McConaughy et al., 1983) have been developed and validated separately for individual classes of substances.

5.2. Developing common outcome measures for heterogeneous samples

In expanding outcome analysis beyond a single targeted substance, strategies are needed to deal with two general issues: (a) developing common outcome assessments for subjects who have different principal drugs of abuse; and (b) considering the subjects' pattern of substance abuse in outcome analyses.

One general strategy for managing multiple patterns of substance abuse in clinical samples entails focus on a single 'principal drug of abuse' for each subject and using measures of that type of drug use as the primary outcome measure. The simplest choices for a common outcome measure in this case would entail frequency measures such as number of days of substance use, percent days abstinent, percent of urine specimens positive or duration of complete abstinence for the principal abused substance. In particular, 'percent days of abstinence' has been adopted as a key outcome variable in major trials of a variety of types of substance use, including alcohol (Project Match Research Group, 1997), cocaine (Crits-Christoph et al., 1999) and marijuana (MTP Research Group, submitted for publication).

The major drawback to these common frequency measures is a loss of sensitivity in measuring reduction in daily amount without the elimination of substance use. This limitation is particularly important for legal substances such as alcohol, for which non-abstinent treatment goals may be set and quantity of use can be accurately reported. If abstinence-related measures are considered insufficiently sensitive to characterize outcome, alternative assessment strategies could entail use of global severity rating for the different substances of abuse or statistical transformation of different types of ratings into a common metric (e.g. z score transformations) (see Schouten, 2000). In the alcohol treatment literature, some reports of composite scores, taking into account both frequency and quantity data, have been proposed (Cisler and Zweben, 1999; Babor et al., 1994).

Combining ratings made across different substances may need to take account of dependence severity or disabilities associated with different classes of substances. The most straightforward assessments of all classes of substances concentrate on frequency measures, such as percent days abstinence from all substances, duration of total abstinence from all substances or time to first drug use of any type. Such total abstinence-oriented measures are adequate when (a) the patients are truly polysubstance abusers with no predominant drug of abuse or (b) in clinical situations in which abstinence from all psychoactive substances is the agreed-upon treatment goal. In other instances, the total severity of current substance use may be more adequately captured through global ratings derived from combining indices of substance problems, such as the ASI drug composite score (McLellan et al., 1985; Alterman et al., 2000) or from patient or clinician judgment, such as the Clinical Global Impressions (CGI) Scale (Dahlke et al., 1992) or the Global Assessment Scale (Endicott et al., 1976). These varied strategies typically entail exchanges in strengths between reliability, in which frequency measures excel, or sensitivity for change measurement, in which global ratings are most useful.

5.3. Dealing with 'noise'

With these issues in mind, development of a new set of measurement and data analytic strategies are necessary to move beyond a focus on the principal substance of abuse to take into account changes in each patient's total pattern of substance use. For example, a patient

may improve in some types of substances but not others, or may substitute heavy use of a secondary substance while decreasing use of one or more targeted substances. Within clinical research trials, capturing the full range of substance use is made even more difficult by varying sample sizes that use any particular substance. These adjustments in most cases reduce statistical power and necessitate a larger overall sample (see Schouten, 2000). Very large sample sizes would be needed to detect significant changes in use patterns of a large number of different substances, especially given the variety of multiple use patterns, such as some cocaine dependent patients who only use cocaine, versus those who use cocaine plus alcohol, versus those who use cocaine plus marijuana, and those who use cocaine plus alcohol and marijuana. To detect changes in use patterns of any of these drugs in response to an intervention requires sufficient numbers of patients with each of the patterns of use and introduce the added complications of multiple comparisons, which have been discussed in detail elsewhere (see Lin et al., 2000; Pocock, 1997; Schouten, 2000).

As noted above, different frequencies and patterns of substance use across the different classes of substance use may be a particular challenge in evaluating meaningful change when heterogeneous samples are included in particular trial. Simple ANOVA based models, while sufficient to evaluate comparatively simple outcomes such as rates of complete abstinence, clearly lack the ability to deal with complex differences in frequency and rates of change across different classes of substance use. A possible strategy for managing the increased variability associated with natural differences in the rates of change by drug type may be the use of random effect regression models (Bryk and Raudenbush, 1987; Lin et al., 2000). A key advantage of these models is that they would allow for both the intercept (baseline frequency of use) and slope (rate of change) to be random variables, and correlations among different outcomes within the same patient could be accommodated using random effects (see Sammel et al., 1999; Lin et al., 2000). Such an approach, which would allow the intercept and rate of change to vary by subject, would better represent the complexity that comes with greater heterogeneity and reduce bias associated with random distributions of drug of abuse across treatment conditions.

Furthermore, abuse of different classes of substances is commonly associated with clinical and social factors (e.g. age, degree of deviance, substance-related impairments). Each of these factors may have a major independent impact on treatment outcome or a specific relationship to the patients' response to the particular study treatment. These differences necessitate adjustments in the study design to ensure balance of drug abuse types across treatment groups. Strategies for patient assignment and analyzing prognostic significance of patient heterogeneity also require consideration of statistical power issues. Patients can be randomized based upon certain key characteristics, such as baseline drug use characteristics or other variables hypothesized to be associated with outcomes. In this manner, the experimental groups would be balanced on key characteristics. The more variables upon which the groups are stratified, however, the greater the need for a large sample size. Methods such as urn randomization could also be used to promote equal distribution of individuals with different types of drug use and related prognostic variables across treatment groups. In urn randomization, an algorithm modifies ongoing randomization probabilities based on prior composition of treatment groups, maximizing multivariate equivalence of treatment groups (Stout et al., 1994). Thus, urn randomization offers the benefits of balancing allocation of important prognostic variables in treatment groups, while still retaining other benefits of random assignment (Wei, 1978).

6. Conclusion

To maximize the scientific yield of substance abuse clinical trials research and to facilitate ultimate community use of empirically validated treatments (Hohmann and Shear, 2002), we

recommend that investigators consider moving away from a single drug focus in three ways. First, include systematic assessment of a wide range of psychoactive substance use throughout the trial and evaluate the impact of study treatments on use of all classes of drugs as part of routine testing for efficacy and safety. Second, except where contraindicated, include patients who use and abuse multiple classes of substances even in trials evaluating treatments of a single targeted drug. Third, consider inclusion of polysubstance abusers or those who primarily abuse multiple classes of substances in the same clinical trial. While focusing on a single class of drugs reduces ‘noise’ and simplifies outcome assessment, these advantages are counterbalanced by limitations in recruitment feasibility and generalization of study findings. Although many treatment efficacy questions can best be answered by single focus studies, we recommend that such designs be adopted only after less restrictive designs are first considered.

Acknowledgments

Support was provided by NIDA grants P50 DA0924, U10 DA13038, R01-DA13444, R29-DA12056, P50-AA01510, K05 DA00089 (to BJR), K02 DA00248 (to KMC) and the VA New England MIRECC.

References

- Alterman AI, McDermott PA, Cook TG, Cacciola JS, McKay JR, McLellan AT, Rutherford MJ. Generalizability of the clinical dimensions of the Addiction Severity Index to nonopioid-dependent patients. *Psychol. Addict. Behav.* 2000; 14(3):287–294. [PubMed: 10998954]
- Anton RF, Drobos DJ. Clinical measurement of craving in addiction. *Psychiatr. Ann.* 1998; 28(10):553–560.
- Babor TF, Longabaugh R, Zweben A, Fuller RK, et al. Issues in the definition and measurement of drinking outcomes in alcoholism treatment research. *J. Stud. Alcohol Suppl.* 1994; 12:101–111. [PubMed: 7722986]
- Babor TF, Steinberg K, Anton R, Del-Boca F. Talk is cheap: measuring drinking outcomes in clinical trials. *J. Stud. Alcohol.* 2000; 61(1):55–63. [PubMed: 10627097]
- Ball, JC.; Ross, A. The effectiveness of methadone maintenance treatment. New York: Springer-Verlag; 1991.
- Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychol. Bull.* 1987; 101:147–158.
- Budney AJ, Higgins ST, Hughes JR, Bickel WK. Nicotine and caffeine use in cocaine-dependent individuals. *J. Subst. Abuse.* 1993; 5(2):117–130. [PubMed: 8400835]
- Burling TA, Ziff DC. Tobacco smoking: a comparison between alcohol and drug abuse inpatients. *Addict. Behav.* 1988; 13(2):185–190. [PubMed: 3369328]
- Caetano R, Weisner C. The association between DSM-III-R alcohol dependence, psychological distress and drug use. *Addiction.* 1995; 90:351–359. [PubMed: 7735020]
- Carroll KM. Methodological issues and problems in the assessment of substance use. *Psychol. Assess.* 1995; 7(3):349–358.
- Carroll KM. Relapse prevention as a psychosocial treatment: a review of controlled clinical trials. *Exp. Clin. Psychopharmacol.* 1996; 4(1):46–54.
- Carroll, KM. Combined treatments for substance dependence. In: Sammons, MT.; Schmidt, NB., editors. *Combined Treatments for Mental Disorders: a Guide to Psychological and Pharmacological Interventions. Pharmacological and Psychotherapeutic Strategies for Intervention.* Washington, DC: APA Press; 2001. p. 215-238.
- Carroll KM, Rounsaville BJ, Bryant KJ. Alcoholism in treatment-seeking cocaine abusers: clinical and prognostic significance. *J. Stud. Alcohol.* 1993; 54(2):199–208. [PubMed: 8459714]
- Carroll KM, Nich C, Ball SA, McCance E, Frankforter TL, Rounsaville BJ. One-year follow-up of disulfiram and psychotherapy for cocaine–alcohol users: sustained effects of treatment. *Addiction.* 2000; 95(9):1335–1349. [PubMed: 11048353]

- Chick J, Gough K, Falkowski W, Kershaw P, Hore B, Mehta B, Ritson B, Ropner R, Torley D. Disulfiram treatment of alcoholism. *Br. J. Psychiatry.* 1992; 161:84–89. [PubMed: 1638335]
- Ciraulo DA, Sands BF, Shader RI. Critical review of liability for benzodiazepine abuse among alcoholics. *Am. J. Psychiatry.* 1988; 145:1501–1506. [PubMed: 2904227]
- Cisler RA, Zweben A. Development of a composite measure for assessing alcohol treatment outcome: operationalization and validation. *Alcohol. Clin. Exp. Res.* 1999; 23:263–271. [PubMed: 10069555]
- Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken LS, Muenz LR, Thase ME, Weiss RD, Gastfriend DR, Woody GE, Barber JP, Butler SF, Daley D, Salloum I, Bishop S, Najavits LM, Lis J, Mercer D, Griffin ML, Moras K, Beck AT. Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse Collaborative Cocaine Treatment Study. *Arch. Gen. Psychiatry.* 1999; 56(6):493–502. [PubMed: 10359461]
- Cunningham JA, Sobell LC, Gavin DR, Sobell MB, Breslin FC. Assessing motivation for change: preliminary development and evaluation of a scale measuring the costs and benefits of changing alcohol or drug use. *Psychol. Addict. Behav.* 1997; 11(2):107–114.
- Cunningham-Williams RM, Cottler LB, Compton WM, Spitz-nagel EL, Ben-Abdallah A. Problem gambling and comorbid psychiatric and substance use disorders among drug users recruited from drug treatment and community settings. *J. Gambling Stud.* 2000; 16(4):347–376.
- Dahlke F, Lohaus A, Gutzmann H. Reliability and clinical concepts underlying global judgements in dementia: implications for clinical research. *Psychopharmacol. Bull.* 1992; 28:425–432. [PubMed: 1296220]
- DelBoca FK, Noll JA. Truth or consequences: the validity of self-report data in health services research on addictions. *Addiction.* 2000; 95(3):S347–S360. [PubMed: 11132362]
- Dunn C, Deroo L, Rivara FP. The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction.* 2001; 96(12):1725–1742. [PubMed: 11784466]
- Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch. Gen. Psychiatry.* 1976; 33:766–771. [PubMed: 938196]
- Fuller RK, Branchey L, Brightwell DR, Derman RM, Emrick CD, Iber FL, James KE, Lacoursiere RB, Lee KK, Lowenstam I. Disulfiram treatment for alcoholism: a Veterans Administration cooperative study. *J. Am. Med. Assoc.* 1986; 256:1449–1455.
- Galen LW, Henderson MJ. Validation of cocaine and marijuana effect expectancies in a treatment setting. *Addict. Behav.* 1999; 24(5):719–724. [PubMed: 10574312]
- George TP, Chawarski MC, Pakes J, Carroll KM, Kosten TR, Schottenfeld RS. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol. Psychiatry.* 2000; 47(12):1080–1086. [PubMed: 10862808]
- Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction.* 1995; 90(5):607–614. [PubMed: 7795497]
- Gossop M, Best D, Marsden J, Strang J. Test-retest reliability of the Severity of Dependence Scale. *Addiction.* 1997; 92(3):353. [PubMed: 9219397]
- Greenstein, RA.; Fudala, PJ.; O'Brien, CP. Alternative pharmacotherapies for opiate addiction. In: Lowinson, JH.; Ruiz, P.; Millman, RB.; Langrod, JG., editors. *Comprehensive Textbook of Substance Abuse.* 3rd ed.. New York: Williams and Wilkins; 1997. p. 415-425.
- Helzer JE, Pryzbeck TR. The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *J. Stud. Alcohol.* 1988; 49:219–224. [PubMed: 3374135]
- Higgins ST, Budney AJ, Bickel WK, Foerg FE. Alcohol dependence and simultaneous cocaine and alcohol use in cocaine-dependent patients. *J. Addict. Dis.* 1994; 13:177–189. [PubMed: 7734468]
- Hohmann AA, Shear MK. Community-based intervention research: coping with the 'noise' of real life in study design. *Am. J. Psychiatry.* 2002; 159(2):201–207. [PubMed: 11823259]
- Hubbard, RL. Treating combined alcohol and drug abuse in community-based programs. In: Galanter, M., editor. *Recent Developments in Alcoholism.* New York: Plenum; 1990. p. 273-283.

- Hughes JR, Rose GL, Callas PW. Nicotine is more reinforcing in smokers with a past history of alcoholism than in smokers without this history. *Alcohol. Clin. Exp. Res.* 2000; 24(11):1633–1638. [PubMed: 11104110]
- Institute of Medicine. Bridging the gap between practice and research: Forging partnerships with community-based drug and alcohol treatment. Washington, DC: National Academy Press; 1998.
- Krishnan-Sarin S, Rosen MI, O'Malley SS. Naloxone challenge in smokers. Preliminary evidence of a common opioid component in nicotine dependence. *Arch. Gen. Psychiatry.* 1999; 56:663–668. [PubMed: 10401515]
- Lin X, Ryan L, Sammel M, Zhang D, Padungtod C, Xu X. A scaled linear mixed model for multiple outcomes. *Biometrics.* 2000; 56:593–601. [PubMed: 10877322]
- Lu NT, Taylor BG, Riley KJ. The validity of adult arrestee self-reports of crack cocaine use. *Am. J. Drug Alcohol Abuse.* 2001; 27(3):399–419. [PubMed: 11506259]
- Martin CS, Clifford PR, Maisto SA, Earleywine M, Kirisci L, Longabaugh R. Polydrug use in an inpatient treatment sample of problem drinkers. *Alcohol. Clin. Exp. Res.* 1996; 20:413–417. [PubMed: 8727229]
- McConaughy EA, Prochaska JO, Velicer WF. Stages of change in psychotherapy: measurement and sample profiles. *Psychother. Theory Res. Pract.* 1983; 20(3):368–375.
- McLellan AT, Luborsky L, Cacciola J, Griffith J, et al. New data from the addiction severity index. Reliability and validity in three centers. *J. Nerv. Mental Dis.* 1985; 173(7):412–423.
- McLellan AT, Alterman AI, Metzger DS, Grissom GR, Woody GE, Luborsky L, O'Brien CP. Similarity of outcome predictors across opiate, cocaine, and alcohol treatments: role of treatment services. *J. Consult. Clin. Psychol.* 1994; 62(6):1141–1158. [PubMed: 7860812]
- Miele GM, Carpenter KM, Cockerham MS, Trautman KD, Blaine J, Hasin DS. Concurrent and predictive validity of the Substance Dependence Severity Scale (SDSS). *Drug Alcohol Depend.* 2000; 59(1):77–88. [PubMed: 10706977]
- O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch. Gen. Psychiatry.* 1992; 49:894–898. [PubMed: 1444728]
- Petrakis IL, Carroll KM, Nich C, Gordon LT, McCance-Katz EF, Frankforter T, Rounsaville BJ. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction.* 2000; 95(2):219–228. [PubMed: 10723850]
- Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes and they will come: contingency management for the treatment of alcohol dependence. *J. Consult. Clin. Psychol.* 2000; 68:250–257. [PubMed: 10780125]
- Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. *Control. Clin. Trials.* 1997; 18:530–545. [PubMed: 9408716]
- Project Match Research Group. Matching alcoholism treatments to client heterogeneity: project MATCH post-treatment drinking outcomes. *J. Stud. Alcohol.* 1997; 58:7–29. [PubMed: 8979210]
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *J. Am. Med. Assoc.* 1990; 264(19):1511–1518.
- Rohsenow DJ, Monti PM, Martin RA, Michalec E, Abrams DB. Brief coping skills treatment for cocaine abuse: 12-month substance use outcomes. *J. Consult. Clin. Psychol.* 2000; 68(3):515–520. [PubMed: 10883569]
- Ross HE. Benzodiazepine use and anxiolytic abuse and dependence in treated alcoholics. *Addiction.* 1993; 88:209–218. [PubMed: 8106063]
- Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: getting started and moving on from stage I. *Clin. Psychol. Sci. Pract.* 2001; 8(2):133–142.
- Sammel M, Lin X, Ryan L. Multivariate linear mixed models for multiple outcomes. *Stat. Med.* 1999; 18:2479–2492. [PubMed: 10474154]
- Sanchez CM, Wilkinson DA, Davila R. Empirically based guidelines for moderate drinking: 1-year results from three studies with problem drinkers. *Am. J. Public Health.* 1995; 85(6):823–828. [PubMed: 7762717]

- Schmitz J, Dejong J, Garnett D, Moore V, Waxman R, Linnoila M, Roy A, Lamparski D. Substance abuse among subjects seeking treatment for alcoholism. *Arch. Gen. Psychiatry.* 1991; 48:182–183. [PubMed: 1989574]
- Schouten HJA. Combined evidence from multiple outcomes in a clinical trial. *J. Clin. Epidemiol.* 2000; 53:1137–1144. [PubMed: 11106887]
- Schwartz RH. Urine testing in the detection of drugs of abuse. *Achiv. Intern. Med.* 1988; 148:2407–2412.
- Sobell, LC.; Sobell, MB. Timeline Follow-Back: a technique for assessing self-reported alcohol consumption. In: Litten, R.; Allen, J., editors. *Measuring Alcohol Consumption*. New Jersey: Humana Press; 1992. p. 41-71.
- Solomon KE, Annis HM. Development of a scale to measure outcome expectancy in alcoholics. *Cognit. Ther. Res.* 1989; 13(5):409–421.
- Stout RL, Wirtz PW, Carbonari JP, Del Boca FK. Ensuring balanced distribution of prognostic factors in treatment outcome research. *J. Stud. Alcohol.* 1994; 12:70–75.
- Tsuang JW, Shapiro E, Smith TL, Schuckit MA. Drug use among primary alcoholic veterans. *Am. J. Drug Alcohol Abuse.* 1994; 20:483–493. [PubMed: 7832181]
- Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone and the treatment of alcohol dependence. *Arch. Gen. Psychiatry.* 1992; 49:876–880. [PubMed: 1345133]
- Warner EA, Kosten TR, O'Connor PG. Pharmacotherapy for opioid and cocaine abuse. *Med. Clin. North Am.* 1997; 81(4):909–925. [PubMed: 9222260]
- Wei LJ. An application of an urn model to the design of sequential controlled clinical trials. *J. Am. Stat. Assoc.* 1978; 73:559–563.