RESEARCH ADVANCES IN NEW PSYCHOPHARMACOLOGICAL TREATMENTS FOR ALCOHOLISM

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Research Advances in New Psychopharmacological Treatments for Alcoholism

Proceedings of the Symposium 'Research Advances in New Psychopharmacological Treatments for Alcoholism' Toronto, 4–5 October 1984

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CONTENTS

Research Advances in New Psychopharmacological Treatments for Alcoholism
C.A. Naranjo and E.M. Sellers, eds.

"I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I--
I took the one less travelled by,
And that has made all the difference."

The Poetry of Robert Frost, 1964, p. 105

DRUG TREATMENTS FOR ALCOHOLISM: THE NEED FOR INNOVATION

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Why are we having this conference? It is our impression that important changes have occurred in this area in recent years which are not in the common domain of the scientific community. This symposium is, in a way, a follow-up of a previous conference held in London, England in March 1983 sponsored by the Alcohol Education Centre and the Institute of Psychiatry and chaired by Griffith Edwards and John Littleton. They have just published the proceedings which I would strongly recommend you to read (1).

Interest in new pharmacological treatments for alcoholism has slowly but steadily increased in recent years (1-3). Systematic approaches to the problem are still confined to a few groups of researchers, most of whom are represented at this conference. They will present papers dealing with innovative approaches for improving the assessment and treatment of alcohol related problems. However, the pharmacotherapy of alcoholism can still be considered a neglected area.

No innovation is possible unless changes occur. We will briefly review some of the factors that have been retarding innovation in this therapeutic research area. Some of the changes needed to accelerate innovation in the pharmacotherapy of alcoholism are listed in Table 1.

TABLE 1

CHANGES NEEDED FOR PROMOTING INNOVATION IN THE PHARMACOTHERAPY OF ALCOHOLISM

1.	Attitude
2.	Concepts
3.	Assessment and testing procedures
4.	Design and testing of new drugs

Innovative Drug Treatments for Alcoholism: A Case of Extreme Neglect

Table 2 summarizes some of the alleged reasons for neglecting this area. These opinions have been verbalized throughout the years by a number of people. I must recognize, however, that this is an unscientific, perhaps highly biased, poll, but it helps to illustrate some of the attitudinal problems. The first point is that some state that since drugs and I say in brackets, of abuse, cause the problem. Why do we need another drug, in this case a medication, to solve the problem? The second, is that some segments of society are skeptical about the capability of science for solving problems, thus some state that this may be just another attempt by reductionists promoting a technological fix to a complex phenomenon. Another obstacle is the belief that drugs and alcohol combined always cause problems. A more serious problem is the insufficient knowledge of the clinically relevant mechanisms of alcohol effects, even though substantial progress on the understanding of the basic neuropharmacological mechanisms has been made in recent years. Another argument is the lack of proper methodology for studying drug effects on alcohol intake and actions in humans. In fact, substantial progress has occurred in this area, as we will hear from some speakers, and this is no longer a plausible argument. A common attitude in the alcohol and drug abuse area is the unwillingness of some therapists to question the effectiveness of their treatments because of the implications of this exercise on their own morale and because of the social and political implications of declaring some treatments ineffective or even dangerous. Of course, drug treatment are no exception in this respect. It is also argued that there is a lack of commitment and support by government and the public. However, since the conference in London took place in 1983, and since we are having this conference now and a number of people are thinking about this problem, perhaps a change in this respect has already occurred.

TABLE 2

ALLEGED REASONS FOR NEGLECTING THE DEVELOPMENT OF INNOVATIVE DRUG TREATMENTS FOR ALCOHOLISM

- Prejudices
  - "drugs" ("of abuse") caused problem why do we need another "drug" (medication)?
  - another "technological fix"
  - drugs and alcohol combined only cause problems
- Lack of understanding of the clinically relevant mechanisms of alcohol effects
- Unwilling researchers
  - the problem is too complicated, other areas have greater pay-offs
- Lack of proper methodology for studying drug effects in alcoholics
- Unwillingness to question effectiveness of available treatments (including drugs)
- Lack of commitment and support by government and public
- Lack of commitment by pharmaceutical industry

Another very important limitation is the apparent lack of commitment of the pharmaceutical industry to this area. The ethical innovative pharmaceutical industry is the main (if not the only source) of new therapeutic drugs (4). A major problem for developing new drugs in this area is that, to my knowledge, no drug company has a research program specifically focused on systematically testing drugs for the treatment of alcoholism. However, as you can appreciate from the program, many pharmaceutical companies are now willing to explore this area and many representatives are actively participating in this symposium.

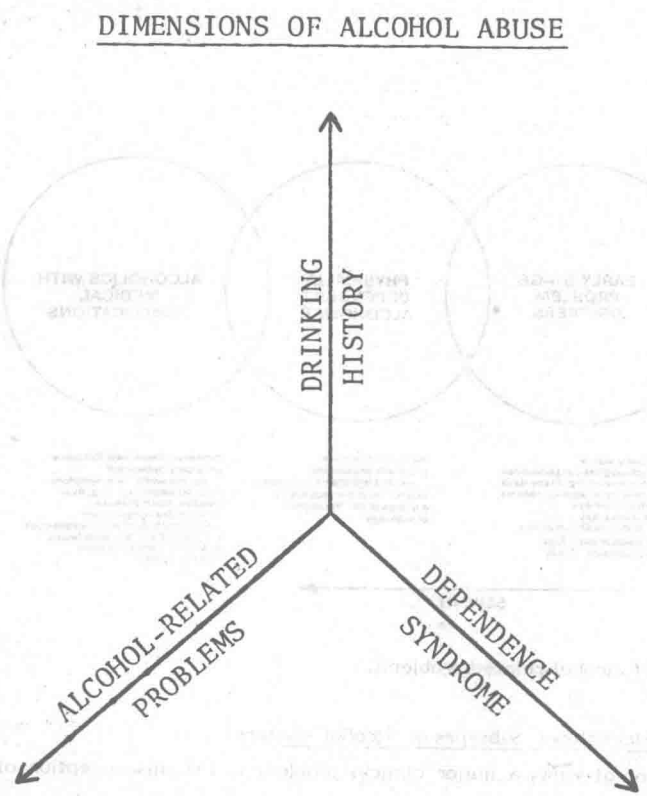

Fig. 1. Dimensions of alcohol abuse.

Willing investigators are needed for testing any research idea, and of course investigators are human and they have their own interest. So some argue that the problem is too complicated, and that with the same amount of effort you can really accomplish more in other research areas. This attitude is usually associated with the belief that alcoholics are hopeless individuals to whom very little can be offered. This pessimistic view can be effectively counter-balanced by important research advances which have identified new leads which are actively being pursued by investigators participating in this conference.

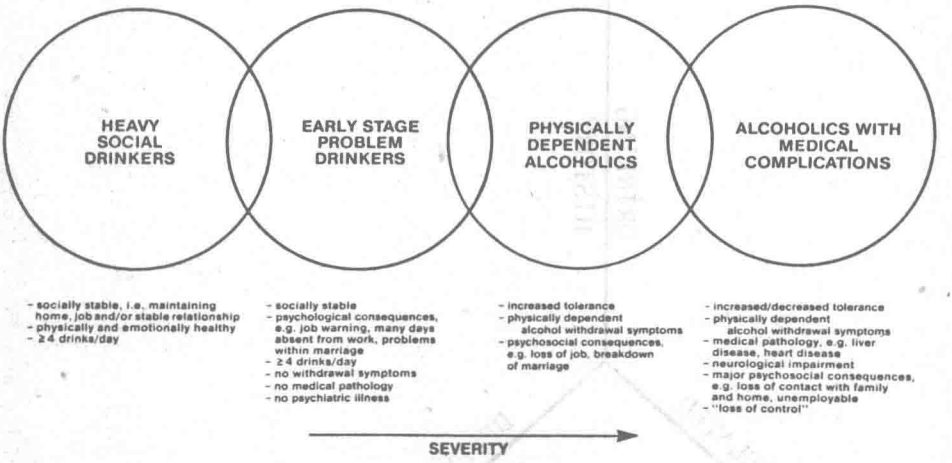

Fig. 2. Clinical spectrum of alcohol-related problems.

The Clinical Spectrum of Alcoholism: Subtypes of Alcohol Abusers

From a conceptual point of view, a major clinical problem is the misconception of considering alcoholics as a homogeneous population. Alcohol abuse is a multi-dimensional condition as represented in Fig. 1. The dimensions are the drinking history, the alcohol dependence syndrome and the alcohol related problems (biomedical and psychosocial). The systematic assessment of alcohol abusers in these three dimensions, generates a

picture that is substantially more complicated than the simple word "alcoholics" suggests. In fact, different subtypes of alcohol abusers emerge depending on the amount they drink, the severity of the dependence syndrome and the problems they present (5). Alcohol abusers include the heavy drinkers, problem drinkers and the alcohol addicts (Fig. 2). These subtypes may respond differently to treatments. Another aspect to consider is that a number of studies indicate that the prevalence of the different subtypes in a population is as follows: alcoholics (5%), problem drinkers (20%), social drinkers (60%) and abstainers (15%) (5). Therefore, it is reasonable to question whether too much attention has been paid to the 5% of classic alcoholics to the detriment of the other subjects. So perhaps it could be appropriate to shift priorities towards the early identification and early intervention of problem drinkers who are subjects with a greater chance of recovery and who represent a large proportion of the alcohol abusers (6).

Most Serious Blocks to Progress: A Personal View

A number of factors which block progress in this area are summarized in Table 3.

TABLE 3

MOST SERIOUS BLOCKS TO PROGRESS: A PERSONAL VIEW

1. Disconnections
2. Dissociation of basic and human research
   - animal models
   - insufficient knowledge about the clinically relevant neurobiological mechanisms regulating alcohol drinking
3. Lack of systematic research
   - few leads should be persued
   - more rigorous clinical science is needed
4. More support needed to achieve critical mass of clinical scientists

Disconnections. A major impediment for developing new pharmacological treatments for alcoholism, is what Griffith Edwards calls the disconnections (7). He talks about three disconnections, I have included a fourth one (Fig. 3, top panel). The diconnections can be described as follows: a group is doing what is called basic research, another is doing clinical research and/or clinical practice, the pharmaceutical companies are developing drugs usually for other purposes and we also have the community as represented by the government and by the public. And all these different groups have their own interests with respect to the problem and the communication and interactions between these different groups have not always been as good as they should have been.

Dissociation of basic and human research. One of the major problems is an apparent dissociation between basic and human research with respect to the development of pharmacotherapies for alcoholism. And one of the aspects where this is more evident

concerns what is considered a valid model of alcoholism or drinking behaviour. For example, the current conceptualization of an animal model of alcoholism (e.g. as presented by Lester and Freed (8)) does not take into account the clinical spectrum of alcohol related problems mentioned above. This is a serious pitfall. In addition, a most serious limitation of these kinds of criteria is the lack of consideration of an essential requirement: the cross-validation of the model by comparing results in animals and in humans. This is very rarely done, and researchers should be encouraged to undertaken such comparisons. Other considerations concerning animal models will be discussed by another speaker.

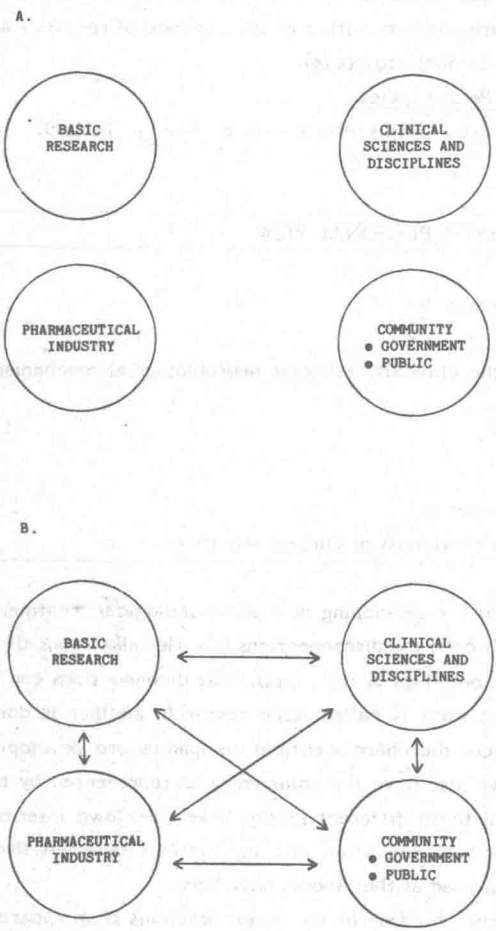

Fig. 3. Current disconnections (top panel) and desirable connections (bottom panel).

It is also important to note that even though numerous studies have been conducted in animals, the concepts emanating from such experiments usually have not been translated into clinically relevant hypotheses to be tested in humans. Therefore, it is necessary that the existing leads concerning possible effects of drugs on alcohol problems be pursued by the appropriate human studies. And also, there is a plea for more rigorous clinical science so that every time a study is conducted, valid conclusions can be reached. Finally, no area of innovation succeeds unless a critical mass of individuals who are willing to exchange ideas and to take risks exists. This can only be achieved by stimulating the connections. We need to stimulate the dialogue between these different groups, so that they can identify the relevant issues, and can proceed with the required experiments (Fig. 3, bottom panel).

Neglect by the Pharmaceutical Industry

The apparent lack of interest of the pharmaceutical industry in this area has been previously emphasized (2,3,7). Since a number of representatives of the pharmaceutical industry are attending this symposium, this message may have a chance of finding a receptive ear. The situation is very puzzling. Pharmaceutical companies continue to spend millions of dollars in developing new anxiolytics and diuretics even though the prototype drugs (i.e. diazepam and furosemide) are very effective. Nowadays there are more than 25 marketed benzodiazepines. But I always ask the question what is new? What is different? Why do they produce more? Diazepam is quite good. So unless somebody shows that the new drug is substantially better in clinically relevant terms, it is reasonable to question whether there is a need to continue spending funds for those purposes. Another contradiction is that there is no relation between the amount of effort and expenditures in research and the relative size of the market. Alcohol related problems are substantially more prevalent than other conditions in which substantial investments are made. Also important to mention is that since there is no company which is developing drugs for this specific purpose, clinical investigators usually have to borrow drugs that are developed for other indications in order to conduct their experiments. I believe improvements in all these areas are possible. For example, systematic research programs by pharmaceutical companies in this area aimed at discovering and clinically testing new drugs for alcohol-related problems could prove very fruitful, and they certainly would provide a major impetus to this research.

Setting Up Realistic Priorities

Some people might still be skeptical about what drugs can achieve for improving the therapy of alcoholism. Examples already exist of treatments which have been proven effective or which constitute hopeful leads. They are summarized in Table 4. Drugs can alleviate symptoms of alcohol withdrawal when used with strategies based on sound pharmacodynamic and pharmacokinetic principles (9,10). Other investigators have shown that the symptoms of alcohol intoxication can be attenuated (11). Studies at NIAAA have

shown that the memory impairments induced by alcohol can be attenuated by some drugs (12,13). There are a few examples of drugs that can moderate ethanol intake (14). There are also a few examples of drugs that can attenuate alcohol-induced organic damage (e.g. liver damage) (15). And of course, there are examples of drugs that can alleviate associated psychiatric illnesses (16). So we are not talking about a fantasy, we already have examples of effective agents. The task is how to optimize our efforts and to accelerate progress.

TABLE 4

SETTING UP REALISTIC EXPECTATIONS

Alcohol-related problems that could be corrected by drugs:

- alcohol withdrawal syndrome
- alcohol intoxication (amethystic agents)
- memory impairments
- moderation of ethanol intake
- alcohol-induced organic damage, e.g. liver disease
- associated psychiatric illness, e.g. depression, mania

Goals of this Symposium

The first goal is the diagnosis of the current status of the field. The second task for this group is the identification of the relevant methodological issues in animal and human research. Also, since resources are limited, priorities in research must be identified. We expect that a fruitful exchange of ideas will occur. Finally, the gathering of individuals who are working in the same area usually has a reinforcing effect. And perhaps from the exchange of ideas, areas of potential collaboration could develop. Very important--we also want, and I insist, to have the conference as an inspiration point for stimulating other researchers to seriously consider this area. And to emphasize this point I will end up by quoting Robert Frost again--sometimes taking the road less travelled could make the difference.

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