

Status Report Concerning the Use of Megadose Nicotinic Acid in Alcoholics

Russell F. Smith, M.D.¹

Five years ago we completed and reported a longitudinal field trial of large-dose nicotinic acid in 500 diagnosed alcoholics over the preceding five years. Ten percent of this sample group was highly motivated, physically and emotionally intact, early intervention alcoholics. Forty percent were alcoholics demonstrating advanced physical symptoms and significant loss of personal and financial resources. The final group was classical "low-bottom" alcoholics showing serious physical, personal, and economic complications of the alcoholic disease. In this diverse group nicotinic acid showed definite potential for benefiting the alcoholic, particularly those demonstrating more serious central nervous system symptoms of the disease.

Several important observations were possible from this study.

Nicotinamide proved of no value to alcoholics, suggesting perhaps another mechanism of action than that proposed for its effects on schizophrenics.

Nicotinic acid improved sleep patterns, mood stability, and overall functioning in 60 percent of the test group who showed the more serious organic symptoms of the disease.

Nicotinic acid significantly reduced acquired tolerance to alcohol.

Nicotinic acid appeared to significantly shorten the course of the acute toxic brain syndrome.

Nicotinic acid all but eliminated "dry drunk syndrome," hyperexcitable, manic episodes, and serious, potentially suicidal, depressions.

A significant part of the sample, particularly those less physically ill, demonstrated possible placebo effect.

These observations strongly suggest a significant beneficial pharmacological effect by nicotinic acid in the more seriously ill alcoholic and little or placebo effect in those not demonstrating significant organic deterioration from alcohol.

This fairly obvious difference in response strongly suggests that other symptoms and mechanisms most likely exist which need to be studied and defined. The impact of placebo effect in a highly suggestible population of practiced "magical thinkers"

P.O. Box 518, Whitmore Lake, Michigan 48189. Prepared for the Canadian Schizophrenia Foundation annual meeting June 4, 1977, Windsor, Ontario, Canada.

also needs to be evaluated. The slow onset of effect and gradual buildup also suggests other unknown mechanisms. Certainly further study is warranted in this area on the basis of this clinical trial. To answer the questions raised by the field trial several factors need to be considered in the development of new protocols.

A theoretical base needs to be developed that can be used to measure past and future studies and permit the development of more relevant, complete, study criteria of measurement.

Expanded, more comprehensive criteria of measurement need to be developed.

Barriers to true blind study of nicotinic acid need to be defined and removed.

The most promising theoretical base at this point in time appears to lie in the metabolism of 5-OH-tryptamine, or the monoamine oxidase reaction. The cerebral catecholamines have already been implicated in previous work with schizophrenics. An adrenochrome or serotonin-chrome has been postulated. Although some of the phenomena observed in our study could be related to a DNA mechanism, the observed effects were much more global and occurred too quickly in many cases to be confined only to this theoretical base. The breakdown of 5-OH-tryptamine into serotonin, dopamine, noradrenalin, and nicotinic acid explains all of the presently observed phenomena far better. These psychoactive substances have now been shown to be responsible for sensory perception, sleep, appetite, mood, and alertness among other important and vital functions. Levels of these biogenic amines are regulated both at the site of production and through controlled degradation to inactive metabolites through the monoamine oxidase reaction. It should again be emphasized that nicotinic acid is a normal byproduct of this important body reaction.

In theory we find the 5-OH-tryptamine mechanism most compatible with observed and reported phenomena regarding nicotinic acid in alcoholics. Nicotinic acid is a simple molecule capable of passing the blood-brain barrier. This fact alone could* explain the failure of nicotinamide to significantly benefit alcoholics.

The saturation of the CNS nicotinic acid mechanism could inhibit 5-OH-tryptamine metabolism reducing levels of serotonin, dopamine, and noradrenalin. Nicotinic acid is a proved histamine stimulant. High levels of histamine tend to inhibit the monoamine oxidase reaction causing reaccumulation of the biogenic amines. Nicotinic acid could well be a biochemical governor regulating in a very significant way the metabolic levels of the cerebral catecholamines.

The role of these catecholamines in alcoholics is now being actively explored and defined. Research has confirmed their part in sedative tolerance and withdrawal symptoms. The implication of these bioactive substances in both healthy and pathological drinking makes this theoretical approach all the more credible.

The emergence of nicotinic acid as the only form of the vitamin effective in alcoholics further complicated our planning for future research. To develop a true placebo for a blind study we had to deal with and compensate for the unpleasant histamine start-up symptoms. Nicotinic acid causes the release of all stored body histamine from the mast cells and other sources. This produces vascular dilatation of the skin causing warm flushing of particularly the neck and head. The same mechanism causes intestinal upset as well. The changes in liver metabolism that affect diabetes and other rare problems associated with chronic use would present no problem since they occur so infrequently that their elimination would not seriously compromise any study.

Only two options exist. First one could put sufficient nicotinic acid in each placebo to cause the histamine start-up symptoms. This approach was discarded because of three important drawbacks. The nicotinic acid required to produce these symptoms might also be active and confuse overall results. The body stores of histamine most likely would not be exhausted as in megadose ranges, and the flushing would persist and continue making the placebo group identifiably different. The subjective symptoms in high- and low-dose nicotinic

acid preparations might be identifiably different. The second option would be to develop or find a form of nicotinic acid that did not produce detectable histamine startup symptoms.

Three years ago we became interested in timed release forms of nicotinic acid as a possible mechanism to minimize or eliminate histamine start-up symptoms. A Miami-based pharmaceutical manufacturer* made available materials in two timed release forms. One form was a multilayered sustained action tablet. Clinical trial of this material demonstrated it to effectively reduce or eliminate the vascular flushing symptoms. Unfortunately the size of the tablet and the dosages required in the alcoholic caused considerable retention of nicotinic acid in the stomach with gastritis and gastric symptoms too severe to be ignored, but certainly not dangerous. We felt this dosage form added little to desirable effect, and at least for the purposes of any proposed megadose study carried with it side effects sufficient to make it readily identifiable.

The second sustained action material is a capsule containing small granules which pass readily through and beyond the stomach. This "spansule" type form of nicotinic acid proved highly satisfactory in field trial. The incidence of histamine startup symptoms are no greater than the symptoms seen in highly suggestible people with inert placebo. This dosage form has been thoroughly tested and is pharmacologically active. Perhaps the most readily measured effect of nicotinic acid is serum triglyceride reduction. The sustained action form was found to be pharmacologically on par with plain nicotinic acid. The manufacturer* has made available equal quantities of active timed release nicotinic acid (Nicobid (R)) and identical inert placebo materials. The key to which material is active or inert has been retained by the manufacturer, permitting a true double-blind cross over study. This study currently underway should permit us to furnish the scientific community the kind of

Key Pharmaceuticals

Evaluation of nicotinic acid's effect it generally requires.

A test track now remained to be developed in

the form of more complete, relevant criteria for the evaluation of nicotinic acid. In a recent study of agents used in alcohol detoxification, symptoms can be developed to monitor serotonin and dopamine effect and others to reflect noradrenalin activity.

Serotonin dopamine symptoms include:

- Insomnia
- Night terrors, hallucinations
- Extraocular muscle disturbances
- Anorexia
- Intestinal upset

Norepinephrine symptoms include:

- Tachycardia
- Hypertension
- Muscle tremor
- Seizure
- Agitation

Severe depression It is hoped that by testing nicotinic acid with criteria specifically related to catecholamine chemistry, effect can be more accurately measured. Accuracy is enhanced by the fact that many of the above criteria lend themselves to quantification.

With the major barriers to a blind study of nicotinic acid adequately resolved, a protocol was developed to implement the present study. Selection of a site and test population was simple, since nicotinic acid is most effective in the sickest alcoholics. We are fortunate to have one of the largest facilities for the treatment of advanced "low-bottom" alcoholics in southeast Michigan. This facility treats over 300 alcoholics in the advanced stages of the disease. The average length of stay from four months to a year permits easy follow up and a stable research population.

We have begun the process of assigning alternate patients to lots A or B of nicotinic acid. At the end of six months the niacin source will be reversed. Those receiving active nicotinic acid will be receiving two 400 mg timed release nicotinic acid capsules four times a day for a total daily dosage of 3,200 mg. The field trial indicates this

dosage should be effective. The other group will receive the same number of identical inert placebo capsules.

Serotonin-dopamine and noradrenalin-moderated physical symptoms will be monitored at weekly intervals. At the end of the 12-month study period the code will be broken and response correlated for pharmacological effect. The results of this blind cross over study should provide adequate data on which to base decisions concerning whether more or what types of studies are needed in the future. Even more important observations may permit more accurate selection of candidates for nicotinic acid therapy. Today when lithium is becoming used more and more for similar indications in alcoholics, a safer alternative with more therapeutic margin is highly desirable.

Summary

The current status of niacin research in alcoholics has been reviewed. A five-year field trial of nicotinic acid strongly indicated great potential for benefit in alcoholics. The next logical step was a confirming blind cross over study. Such a study was considered even more

important since it represents the kind of proof acceptable to the scientific community. Three obstacles remained in the way of such a study. Current literature and observations in previous studies permitted the development of a theoretical approach for nicotinic acid effect at the point of 5-OH-tryptamine metabolism. A set of clinical criteria already tested in a previous study based on tryptamine metabolic cycle was developed. A satisfactory test form of nicotinic acid in timed release form was found which eliminated tell-tale histamine start-up symptoms, which permitted identical placebo development. With these significant barriers removed, a blind cross over study has been implemented in a study population selected to demonstrate maximum effect.

REFERENCES

SMITH, R.F.. A Five-Year Field Trial of Massive Nicotinic Acid Therapy of Alcoholics in Michigan Journal of Orthomolecular Psychiatry, Vol. 3, No. 4. 1974.

SEXUS, FA, and ENGLISHIN, S: Alcohol and the Central Nervous System. Annals New York Academy of Sciences, New York, NY, Vol 215. 1973.

GITLOW, S.E., DZIEDZIC, L.M., DZIEDZIC, S.W., and WONG, B.L Influence of Ethanol, on Human Catecholamine Metabolism. Annals of New York Academy of Sciences. Vol. 273, p 263, 1976

SMITH, R.F., and MORIN, R: Prototype Comparison of Clinical Effectiveness of Chlordacypoxide HCl, and Phenobarbital in the Management of Sedative Withdrawal Medical Scientific Session, National Alcoholism Forum Annals of New York Academy of Sciences, Vol 273, p 878. 1976

Publishing Policies

The Academy of Orthomolecular Psychiatry

The Journal of Orthomolecular Psychiatry is an educational journal published quarterly by the Academy of Orthomolecular Psychiatry as a service to the public. Certain classes of memberships to the Canadian Schizophrenia Foundation and the Huxley Institute for Biosocial Research include subscriptions to the Journal and a quarterly Newsletter. To become a member, write to the Canadian Schizophrenia Foundation, 2231 Broad Street, Regina, Saskatchewan, Canada S4P 1Y7, or to the Huxley Institute, 1114 First Avenue, New York, N.Y. 10021. Membership contributions are income tax deductible. Members of the Academy will receive the Journal. Annual subscription rate for the Journal

of Orthomolecular Psychiatry to non-members is \$22, and to libraries \$30.

Copyright 1978 by the Academy of Orthomolecular Psychiatry. All rights reserved. Publisher's written permission must accompany papers published previously in another journal.

The Journal, its editors, and the publishers do not take responsibility for opinions expressed by the authors. The Journal board and editors do not necessarily agree with all the articles that are published.

Send correspondence relating to published issues and annual subscription orders to the Canadian Schizophrenia Foundation, 2231 Broad Street, Regina, Saskatchewan, Canada S4P 1Y7.