Where is Appendix? Specify scales used

THE UNIVERSITY OF CHICAGO

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TO Subcommittee on Guidelines for evaluating Antianxiety Agents DEPARTMENT

FROM Dr. E. H. Uhlenhuth EHU DEPARTMENT Psychiatry

IN RE: Draft of Guidelines

Enclosed are drafts of guidelines addressed to the first three topics: 1) selecting subjects, 2) measuring change and 3) clinical significance. The essay on 4) training raters, might be regarded as representing a guideline, with perhaps some condensation needed. Please note that the Appendix to guideline 2 is currently under development by Natalie Reatig and will follow when ready. It is envisioned essentially as a catalogue describing important properties of the measures listed, so that investigators can choose on the basis of their needs, the information on each measure, and the recommendations of guideline 2.

Dick Wittenborn has offered to write a separate version of the guidelines for antianxiety agents, so that we can have two independent sources for our further thinking. I assume his version will reach you soon, so that you may wish to postpone sending me your comments until then.

The guidelines we produce could take the form of 1) freestanding appendices to the guidelines originally published in the Psychopharmacology Bulletin or 2) a revision of the original guidelines integrating the newer details. Currently I would favor the second alternative, as it would dispense with duplication and possible contradiction and it would set a precedent for frequent, regular revision of the guidelines to incorporate advances in knowledge.

Please let me have your comments as soon as practical.

Best regards.

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SELECTING SUBJECTS FOR TRIALS OF ANTI-ANXIETY AGENTS

The term "anxiety" has many different meanings. In the context of evaluating the therapeutic effects of anti-anxiety agents, "anxiety" refers to states of manifest anxiety. These states are characterized by the following:

Subjective experiences:

1. Feeling nervous, jittery, jumpy
2. Feeling fearful, apprehensive, anxious, panicky
3. Fears of fainting, screaming, losing control, crowds, places, disaster, death
4. Avoiding certain places, things or activities because of fear
5. Feeling tense or keyed up

Muscular or motor phenonomena:

6. Tense muscles, aches
7. Trembling, shaking
8. Restlessness, fidgeting

Autonomic phenomena:

9. Heart beating fast or pounding; chest pain
10. Trouble catching breath, air hunger, smothering, lump in throat, choking
11. Sweating, especially armpits, palms, soles of feet
12. Cold, clammy hands
13. Dry mouth
14. Dizziness, faintness, lightheadedness, weakness
15. Tingling feelings in hands or feet
16. Stomach "gas", nausea, upset stomach
17. Wanting to use the toilet often (urine or bowels)

Patients selected for trials of anti-anxiety agents should show at least the first two manifestations plus several others in the list above. A sufficient quantity of the pathology should be present to warrant treatment and to allow room for improvement. This should be documented by initial scores on one or more of the quantitative criteria of drug effect, which exceed specified levels. Although the specification of minimum levels at this time has to be largely arbitrary, mean levels in normal and pathological samples are available for some measures and can provide guidance (see "Assessment of Change").

Manifest anxiety as described above can occur in association with a variety of other symptoms and in a variety of diagnostic conditions. Anxiety may respond differently to medication in different clinical contexts. Two reasonable strategies are open to the investigator in coping with this problem. First, he may deal with anxiety strictly as a diagnostic entity, i.e., anxiety neurosis, and select his sample accordingly (see diagnostic criteria of Feighner et al). Second, he may deal with manifest anxiety as an affective state occurring under many clinical circumstances and select his sample accordingly. The strategy that the investigator adopts will define the population to which he can generalize his results.

The second strategy should be limited to a diverse group of primarily psychoneurotic patients. Present knowledge suggests that anxiety may respond differently in patients with psychosis, borderline states, severe behavior disorders, addictions, or serious somatic or psychosomatic disorders. Antianxiety agents therefore should be studied separately in these conditions.

The mixture of anxiety and depression, even in psychoneurotic patients, also presents a special problem. Although the two states frequently occur

together in varying degrees, most patients can be classified as primarily anxious or primarily depressed, both on clinical interview and on quantitative measures that assess the two affects. Claims that an agent is effective for both anxiety and depression should be supported by results in primarily anxious and in primarily depressed patients, rather than in some unspecified mixed states.

The response of manifest anxiety to medications depends not only on the accompanying pathology, but also on a variety of circumstances including:

1. Duration of symptoms
2. Age of first onset
3. Number of prior episodes
4. Previous treatment
5. Prior medication
6. "Normal" versus outpatient versus inpatient status
7. Type of practice
8. Age
9. Sex
10. Indicators of social class, such as education and occupation (10)
11. Race

There is also increasing evidence that relatively stable personality traits help to determine patients' responses to anti-anxiety agents. Although definite recommendations cannot be made yet, the investigator may wish to include a measure of personality traits.

The investigator should describe his sample systematically in terms of the above characteristics. He also may employ these patient charac-

teristics in a variety of other useful ways. First, he may limit his sample to patients with specific characteristics, particularly in small studies, where heterogeneity presents the greatest problems. Responsiveness in different age groups can be so variable that children, adults and geriatric samples generally should be studied separately.

Second he may include sample characteristics as independent variables in his analysis of results to provide more precise estimates of drug effects, to learn more about the effects of the sample characteristics themselves, and to delineate the most responsive subsamples. This tactic is especially well adapted to large studies where each characteristic is likely to be well represented over a wide range of values.

The issue of overriding importance is this: claims of effectiveness should be confined to the conditions and samples actually studied and should be supported by well-specified documentation.

ASSESSMENT OF CHANGE IN TRIALS OF ANTI-ANXIETY AGENTS

In setting up a clinical trial, the selection of criteria for evaluating treatment response is crucial. Pertinent areas for assessment include the patient's subjective experience or symptoms; his functional status, social adjustment or role performance (worker, spouse, parent, etc.); his physiological status; and his performance on a variety of specific tasks. Possible observers of the patient's condition include the patient himself, other family members or friends, the treating clinician, other professionals participating in the patient's care, such as nurses, and independent research raters.

Specific classes of criteria that have been found useful in evaluating antianxiety agents include:

1. Global rating scales.

Global rating scales can be used by various observers to summarize the patient's condition. The condition to be rated and the time period covered should be clearly specified. The ends of the scale should be well defined. The number of points offering maximum discrimination is not well established.

Two types of global rating scales are in common use. The one refers to the patient's present status (absolute) on a seven-point scale ranging from no pathology to most severe pathology, as measured against the rater's entire previous clinical experience.

The other global scale refers to the patient's change since the start of treatment or since the last visit (relative) on a seven-point scale ranging from marked worsening (-3) through no change (0) to marked improvement (+3).

2. Symptom rating scales.

A number of standardized rating instruments are available for pa-

tients, clinicians or other observers to record the intensity of many symptoms associated with psychoneurotic states, including anxiety and depression. Some of these scales assess several dimensions in a common metric.

3. Target symptom ratings.

These measures represent a special case of the more general approach to rating symptoms. They provide a tailor made instrument for the individual patient: the chief symptoms presented by the patient at the beginning of treatment are rated for their intensity initially and through the course of treatment. The key complaints can be selected by patient or clinician, and ratings can be made by the corresponding observer. Although these ratings have high relevance to the individual patient, group analyses encounter the problem of mixing dissimilar symptoms.

4. Mood adjective checklists.

These measures provide quantitative assessments of various mood dimensions, including tension/anxiety and depression. Usually they are rated by the patient, although they can be used by other observers as well.

5. Indirect verbal measures.

These measures provide estimates of affective states and other areas of function through content analysis of spoken or written verbal samples from the patient, by carefully trained technicians according to procedures specified in detail. Although these procedures are less subject to some of the distortions encountered in direct measures, they are difficult and time consuming.

6. Ratings of social adjustment.

These measures cover such areas as work performance, interpersonal

relations, and function as a spouse and parent. Some are designed primarily for use by a relative, but the clinician or the patient himself may rate others.

7. Indirect clinical measures.

These measures include observations of the clinician's medication guesses, patients' reports of favorable and unfavorable life events, and rates of premature termination and their reasons. Interpretation of such measures tends to encounter problems of clinical relevance.

8. Physiological measures.

These measures address themselves primarily to the level of sympathetic arousal and include heart rate, respiratory rate, skin resistance or potential, forearm blood flow and palmar sweating. EEG patterns also have been employed to identify drug effects. Although these measures offer greater objectivity, interpretive problems remain with regard to clinical relevance.

9. Behavioral measures.

These measures address themselves to such functions as non-discriminated avoidance, conflict behavior, fine motor performance, attention, and information processing rates. These measures also present the advantages of objectivity and the interpretive problems of clinical relevance.

Anxiety states by definition are primarily subjective. Functional disturbances associated with anxiety usually are less marked than in other conditions. The relationship between clinical anxiety levels and more objective physiological and behavioral measures is not well established. The patient generally takes the initiative in seeking, maintaining and terminating treatment. Treatment contacts generally are on an ambulatory basis and limited to a single clinician. On account of these circumstances, the

most important and practical measures of anxiety states focus on symptoms as evaluated by patient and treating clinician.

Criteria of drug effects in clinical trials of antianxiety agents should include at least a global rating and a standardized symptom rating by the clinician, as well as an independent standardized symptom rating by the patient. It is desirable for additional measures to be included also.

In selecting specific measures, the following properties of each measure should be considered:

1. Reliability.

Reliability refers to the consistency of measurement. Measures that remain very stable over long periods of time are likely to tap characterological traits rather than affective states amenable to medication. Consistency on repeated occasions over brief time periods and among multiple observers on the same occasion are clearly desirable.

2. Validity.

Validity refers to the ability of the measure to reflect the property of interest, in the present case anxiety. The most practical test of a measure's validity in this situation is its demonstrated ability to discriminate the effects of anti-anxiety agents.

3. Comprehensivenss of content.

It is useful for a measure to provide estimates of clinical parameters besides anxiety, especially depression and psychotic trends, in order to define quantitatively the context within which anxiety is being studied, to document exclusion criteria, and to reveal other potential drug effects. Although separate instruments can serve these purposes, a common

metric has the advantage.

4. Normative data.

Normative data on patient and non-patient samples aid the investigator in a) setting minimum levels of anxiety for including patients in his study, b) setting maximum levels of other pathology acceptable for including patients in the study and c) interpreting the effectiveness of treatment in reducing pathology.

5. Ease of administration.

Measures requiring less time and effort on the part of the observer, particularly the skilled professional, have the advantage. Measures designed for patient self-report are more effective when comprehension requires minimal education. This involves both conceptual and linguistic level. More specific items are more readily rated by all observers. Scales with fewer points are easier to rate. Simplicity of scoring is an advantage.

The attached appendix reviews specific criterion measures in the various classes with respect to the properties listed. The omission of a measure from this catalogue does not reflect any judgment, express or implied, as to its merits.

DRAFT
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EVALUATING DRUG TRIALS IN TERMS OF CLINICAL SIGNIFICANCE

Several excellent discussions are available on the topic of interpreting the results of clinical drug trials. These papers document the many serious problems involved and raise doubt that any specifiable procedure can even begin to take account of the possible contingencies. The following suggestions with respect to specific interpretational problems are offered tentatively:

1. Criteria of drug effect.

Drug trials usually include a variety of criteria, which may respond differently to the drug. Efficacy should be judged in terms of the most central criteria, and these should be specified in advance. They should include the clinician's global rating and the clinician's and the patient's symptom ratings on the dimensions of anxiety and somatization. Non-significant drug-placebo differences or similar mean responses to drug and placebo in a properly designed and executed study should raise doubt about the efficacy of the drug in that study.

Significant drug-placebo differences on criteria not specified in advance should be regarded as heuristic observations that require confirmation in additional studies.

Significant drug-placebo differences should be demonstrable between group means on quantitative ratings. Significant drug-placebo differences also should be demonstrable in the number of individuals showing improvement in each treatment group.

2. Sample size.

Significant drug-placebo differences should be demonstrable in studies with 20-40 patients per medication group, i.e., in a sample size

likely to be encountered in the individual practitioner's caseload.

There is no objection to combining data from several similar studies to increase sample size, if necessary. (In many instances this procedure entails increases in heterogeneity which more or less offset the gains in numbers). A collaborative study, however, does not obviate the need for replication of results.

3. Number of studies.

Five well designed and executed studies of 40-80 sample size should suffice for the demonstration of efficacy. When the patients selected are reasonably homogeneous as to clinical picture, more than half the studies should show statistically significant ($p < .05$) drug-placebo differences, and all studies should show differences in the expected direction.

4. Comparison with standard drug.

The new anti-anxiety agent should not be significantly less effective than a standard medication, such as chlordiazepoxide or diazepam, in two three-group studies which also demonstrate significant drug-placebo differences in favor of the new drug.

5. Amount of improvement.

The case for clinically significant efficacy is strengthened if the amount of improvement with the new medication is substantial. The following observations on the major measures of pathology provide supportive evidence: 1) The new medication reduces pathology substantially more than placebo in terms of the scale in question. 2) The new medication reduces pathology to a level near the general population norm. 3) The drug-placebo difference accounts for at least 5% of the total variation in outcome.