A Consensus Meeting on Effective Research Practice in PTSD

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ABSTRACT

The aim of this meeting was to obtain a consensus on what constitutes good research practice in posttraumatic stress disorder (PTSD). Objectives were to review relevant parameters of trials, such as the patients recruited, the means of assessing PTSD at baseline, and the change in symptomatology in response to treatment, and to reach a consensus on the most appropriate parameters to use in future research. The bases for the discussion were the 1995 National Institute of Mental Health (NIMH) and the National Center for PTSD consensus on the assessment of PTSD, results of drug treatment trials, and information on the assessment scales used in PTSD research.

PTSD OUTCOME CRITERIA—THE 1995 NIMH/NATIONAL CENTER FOR PTSD CONSENSUS

This consensus group of the National Center for Posttraumatic Stress Disorder (PTSD) and the National Institute of Mental Health (NIMH) was convened to work on issues in the assessment of PTSD. The aims of the meeting were to provide some standardization and guidelines for the field of PTSD research. Five aspects of PTSD were discussed: PTSD assessment in research studies; assessment of stressors (criterion A); evaluation of comorbidity; evaluation of adjustment, functioning, and quality of life; and evaluation of children with PTSD (which is not discussed in the present report).

ASSESSMENT OF PTSD

Recommendations on the assessment of PTSD were as follows: The traumatic event should be described and measured separately, in terms of exposure to it (A1) and the reaction to the exposure (A2), in order to ascertain whether or not A2 is an important element in the overall development of the disorder. In addition, symptoms of reliving the experience (B) and avoidance (C) should be linked to the event itself. In this way, it should be possible to ensure that the events reported reflect the presence of PTSD and not some other psychopathology. In those patients who have been exposed to multiple traumatic events (most patients), it is appropriate to rate three of the events and their possible relationship to the presence of PTSD.

When assessing PTSD, both the frequency and severity of symptomatology should be taken into account. Episode duration should also be assessed to aid understanding of the course of the condition. Levels of distress and their associated levels of impairment are also important, and should be included in the assessment of severity of the condition. For intensive studies of PTSD, a structured diagnostic interview should be used by the clinician, for example, the clinician-administered PTSD scale (CAPS), the Structured Interview for PTSD (SIP), or the PTSD Symptom Scale. The interview should also, as these three do, give both a dichotomous rating of absence or presence of PTSD, and a continuous rating of disease severity. The structured interview used should have strong interrater and test-retest reliability, internal consistency, high content validity, demonstrated usefulness across different traumatic events, and validity in different study populations. Ideally, manuals and videotapes should be available for training on the assessment instruments.

THE ASSESSMENT OF STRESSORS

In defining stressors, careful, behaviorally anchored terminology should be used, and jargon that is imprecise and not universally understood should be avoided. When measuring the stressor, exposure should be measured independently of the symptoms exhibited in reaction to the exposure. The timing of the reaction to exposure should be measured, as this reaction may occur long after the initial trauma is experienced. Data are also required on the presence of dissociation as a reaction to exposure. Even in apparently homogeneous populations of patients, it is generally important to screen for a wide range of traumatic events, as most patients have experienced more than one event. It was recommended ▶

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that a set of carefully worded items that covers a range of types of traumatic events be used as a minimum screening tool. An evaluation of the range of traumatic experiences that a patient has experienced may help to define why or why not particular patients respond to treatment.

ASSESSMENT OF COMORBIDITY

It was felt that treatment response may often be strongly influenced by the presence or absence of, and different types of, comorbidities. Therefore, it was recommended that all types of studies should make broad assessment of comorbidities in the patients included. In addition, decisions on whether comorbidities are part of the primary diagnosis of PTSD, or are secondary to the condition, cannot be made until extensive data on comorbidities are collected. Certain populations of patients with PTSD are known to carry a high burden of comorbidity, and systematic study of these will aid understanding of the differences in PTSD between these groups, and differences in their response to treatment. It was strongly recommended that a general self-reporting, dimensional measure of psychopathology be used, such as the GHQ or the SCL-90. Clinician interviews should also be used when feasible, focusing on the Axis 1 disorders.

ASSESSMENT OF ADJUSTMENT, FUNCTIONING, AND QUALITY OF LIFE

The assessment of social, psychological, and physical health status is essential in all studies of PTSD. The degree of detail of assesment varies, depending on the specific aims of particular studies. Socioeconomic status should obviously be studied, along with family, marital and sexual functioning, social support, and legal involvement. Psychological dimensions that should be studied include demoralization, nonspecific distress, life satisfaction, quality of life, coping mechanisms, risk taking/avoidance, spirituality, and the meaning patients attribute to their life. Measurement along all three domains of adjustment, functioning, and quality of life can be acheived with a single or multiple instruments.

RECRUITMENT OF PATIENTS TO PTSD TRIALS

Types of Trauma Experienced

In the large trial conducted by van der Kolk et al[1] of fluoxetine and placebo, despite a significant effect in favor of the active treatment, the type of patient had a stronger influence on treatment outcome than did the treatment received. Civilian patients recruited to a trauma clinic showed a much larger response to treatment than did combat veterans recruited from the Veterans Affairs Clinic (VAC). This may result in a reluctance to recruit combat veterans to treatment trials, in the belief that they are difficult to treat. More accurately, patients in the VAC have other features, such as the chronicity of their disorder, greater comorbidity, and their reliance on compensation for PTSD, that may affect their treatment outcomes.

The consensus of the group was that veteran patients (who constitute a large proportion of male patients) do respond to treatment, and should not be excluded from trials. Instead, attempts should be made to produce a definition of treatment refractoriness, and to exclude from trials the patients who fulfill that definition. It may also be that these patients are best addressed in separate trials specifically for this population. Another approach might be to recruit veterans who are not part of the VAC, for example by referrals from medical clinics of patients with long-term stress-related conditions such as irritable bowel syndrome and cardiovascular disease.

Patient Motivation for Recruitment

Many factors clearly influence the patient's motivation for recruitment to a trial. These include their past experience of health care, the range of therapeutic choices available, and the nature of their health care system. Combining results from different health care systems (eg, health care paid for by the patient in the USA, with free health care received by veterans, or the free health care available in some European countries or Australia) may introduce different selection biases in the patients recruited, which affect treatment outcome. Likewise, patients recruited from large cities, in which there are many specialist clinics and therefore several therapeutic options available to the patient, will differ from those who live in small communities with limited options, and from those such as veterans, whose care is closely delineated by the VAC.

It can be difficult to ascertain the backgrounds of patients recruited via newspaper advertising, and therefore to produce homogeneous treatment groups. A more useful means of recruitment of patients may be via private practices associated with trauma clinics. Such patients are clearly treatment seeking and their background is documented. However, such patients are usually receiving psychotherapy and this must be taken into account in the trial design. The group consensus was that patients receiving trauma-focused therapies, that is, any therapy that is directed toward anxiety reduction, should be excluded but supportive psychotherapy should be allowed, provided it is initiated before the start of the trial and is maintained throughout in a constant fashion. The type and intensity of this treatment should be quantified for later analysis.

ONGOING COMPENSATION AND/OR LITIGATION

The availability of compensation for the patient's status may well affect response (or nonresponse) to treatment. Despite the fact that some studies have now shown that there are no differences in treatment outcome for patients who do and do not settle litigation, it was suggested that this variable should be excluded as far as possible from clinical

trials. Thus, it was recommended that patients whose continued receipt of financial benefits is contingent upon maintaining PTSD symptoms, or who are awaiting a decision concerning the possibility of receiving financial benefit, should be excluded from clinical trials.

PATIENTS WITH COMORBIDITIES

In the past, studies of other disorders have not stringently taken patients' comorbidities into account. However, comorbidities are extremely common in patients with PTSD, and a great deal of interest has focused on this issue in the discussion of trial design. Because of this interest, it appears that there is a danger that overly stringent standards will be applied to PTSD trials, compared with those in other fields of psychiatry (for example, studies in depression do not usually screen patients for previous trauma and PTSD), making recruitment to the trials unfeasible. Nevertheless, patients' comorbidities must be taken into account, measured, and analyzed for the trial results to be valid.

Comorbid depression is particularly important for several reasons. First, because it affects such a large proportion of patients. Second, it may itself develop as a result of trauma. Third, because it may be a risk factor for PTSD. It is clear that patients presenting depression as an overwhelming feature of their symptomatology should not be included in trials. On the other hand, all patients with comorbid depression cannot be excluded from trials, because the remaining population would not be representative of the overall population of patients with PTSD. In previous trials, the inclusion of patients has been on the basis that major depression is not the primary disorder. However, such a criterion is difficult to operationalize. In addition, it can be argued in such patients that the major effect of treatment is not on PTSD but on comorbid depression. This criticism can be countered, at least in part, by demonstrating efficacy of the treatment on symptoms that are specific to PTSD and not depression, or in subgroups of patients who do not have comorbid depression.

The consensus of the group was that in treatment trials, as "pure" a population of patients with PTSD as possible should be recruited, while recognizing that the average patient with PTSD will have comorbidities. In addition, patients should be excluded whose index trauma was preceded by another psychiatric disorder, which is present at the time of diagnosis or study entry.

RATING SCALES IN PTSD TRIALS

The most common interview-based scales used are the clinician-administered PTSD scale (CAPS), structured interview for PTSD (SIP), TOP-8, clinician's global investigation (CGI), and Duke global rating scale. The self-rating scales are the impact of events scale (IES), the Davidson trauma scale (DTS), the Mississippi scale, and the PTSD Checklist (PCL).

The CAPS

The CAPS-1 was designed as a general diagnostic instrument, by which determinations of current and lifetime PTSD status could be made. The CAPS-2 was designed to assess PTSD symptoms in the previous week, as a brief, repeated assessment. The CAPS provides flexible administration options. Thus, the 17 core symptoms of PTSD, the six criteria for diagnosis of PTSD, and the associated symptoms of the disorder can all be measured. The scale is therefore a multifaceted instrument that can be used to assess the disorder in many different ways: for example, focusing on symptom severity, frequency, intensity, their link with the traumatic event, or the presence of associated features of PTSD.

Reliability of the scale is provided by its carefully phrased initial probes, produced from the consensus of many researchers, optional follow-up probes for common clarifications to allow accurate rating of symptoms, and explicit rating scale anchors with clear behavioral referents. The scoring options are flexible: a dichotomous assessment of PTSD diagnosis can be made, severity of PTSD can be measured as a continuous variable, or assessment can be made in terms of five ranges of symptom severity from asymptomatic to extreme. In addition, an assessment of symptom severity in the past week or past month, and a lifetime as well as the current diagnosis can be made.

Psychometric evaluation of the scale has shown that it has good psychometric properties. Interrater reliability and internal reliability are both good. Correlation with other scales of PTSD is high, whereas that with scales for other psychiatric disorders is low. Correlation with the previous gold-standard scale, the structured clinical interview for DSM-III-R (SCID) is extremely good for presence and absence of the condition. In addition, sensitivity of the scale to changes in response to treatment is good. It is considered a highly valid scale for the following reasons. Ratings made using the scale correspond directly to all the DSM-IV criteria for PTSD. The intensity ratings are based on duration, subjective distress, and functional impairment of the patient. There is explicit assessment of the link between the traumatic event and the patient's symptoms. The items have been developed and devised on the basis of feedback from a broad range of PTSD experts. Use of the scale is now supported by a large amount of research.

The group agreed that the CAPS is an extremely useful tool for the assessment of PTSD. The major objection to using the CAPS is that administration of the full scale is time consuming, and that repeated assessment allows prolonged trauma exposure to patients which may constitute some form of therapy. Nevertheless, a full examination need not be used repeatedly, and simple assessment of the presence of the core symptoms of PTSD on the CAPS takes only a short time.

THE TOP-8 SCALE

The TOP-8 was designed as a brief scale specifically for the assessment of treatment outcome in PTSD.[2] It was developed from the SIP by selecting items from this scale that are the most commonly occurring in patients with PTSD and show the greatest change in response to treatment. The TOP-8 comprises eight items, each measured on a scale of 0-4, with defined anchors given for each item. The items are representative of all four core features of PTSD: intrusion, avoidance, numbing, and hyperarousal. Therefore the scale can be used to produce a measure of severity of PTSD. It can also be used categorically to assess the presence or absence of PTSD or to determine the likelihood of an adequate treatment response. Psychometric assessment has shown that the scale has adequate psychometric properties. Test-retest reliability and internal reliability are good. The score on the TOP-8 correlates well with scores and assessments of severity made using other PTSD-specific scales.

Group consensus was that this scale is a useful addition to PTSD research. It is quick to administer, efficient, and reflects the treatment-responsive elements of the disorder. The brevity of the scale is also, of course, limiting, in that some features of the disorder are not measured at all, so any change in these in response to treatment would not be noted. To complement the TOP-8, the full SIP should also be rated at baseline and endpoint. In addition, the scale has, to date, only been tested in patients receiving selective serotonin reuptake inhibitors (SSRIs) and placebo, and therefore may be inherently biased for the effects of SSRIs. It should be tested across other medications (though most of the pharmacotherapy for PTSD does involve the SSRIs) and psychological interventions.

SCALES FOR USE IN PTSD TRIALS

The consensus of the group was that a full assessment of PTSD should be made at key points during trials, at least at baseline and endpoint, using the CAPS. In this way, the diagnosis of PTSD can be assured, and responses to treatment of all the symptoms and key associated symptoms of PTSD measured. The TOP-8 scale should also be used at regular and more frequent intervals during the trial to assess patients' responses to treatment. These two scales should be used as primary efficacy measures. Secondary measures should include global assessment scales, measures of anxiety and depression, and quality-of-life scales. It was also suggested that patients be assessed for retraumatization and major losses, as these are often associated with relapses of the disorder. CNS

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