

Consensus Meeting

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Post Traumatic Stress Disorder: Guidelines for investigating efficacy of pharmacological intervention

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Introduction

This paper represents the outcome of the deliberations of a group of experts, reporting through a consensus panel, on the recommended methodology for examining the efficacy of treatment for posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) is a pathological response to the experience of a traumatic event. The traumatic event is persistently re-experienced with flashbacks, intrusive thoughts, recurrent distressing recollections, dreams, or the feeling that the traumatic event is reoccurring. Sufferers seek to avoid any of the stimuli associated with the traumatic event, which cause acute distress, be it thoughts, conversations, people or places. They often have a markedly reduced interest in activities, have feelings of detachment or emotional numbing, and the feeling of reduced life expectancy. The individual is in a state of increased arousal and may have sleep disturbance, concentration difficulties, irritability, or exaggerated startle response. The disorder is distressing, often chronic, and interferes substantially with normal function.

PTSD is a relatively common disorder and its prevalence in the general population has been estimated to be between 3 and 6% (Breslau et al., 1991). Many people suffer a major traumatic event in the course of their life, but PTSD develops in only between 10% and 20% of cases. In the National Comorbidity Survey (Kessler et al., 1995) 61% of men and 51% of women reported experiencing at least one major trauma in their lifetime, and in most cases there were two or more events. PTSD developed in 20% of the women and 8% of the men exposed to

traumatic events. However, the prevalence of PTSD is likely to vary between different cultures and according to local historical events.

The likelihood of PTSD increases with the severity of the traumatic stressor and where there is perceived personal threat. In the studies published to date the event most likely to lead to PTSD appears to be rape and this applies to both sexes with rates of 65% in men and 46% or more in women (Kessler et al., 1995). The risk of PTSD is high following events with a serious threat to life or personal integrity, for example in one series rates of 32% are associated with being attacked and badly beaten up, 17% with serious accident or injury, 15% with being shot or stabbed (Breslau, 1998). The risk of PTSD following natural disasters (fire, flood, earthquake etc) is much lower and rates differ little between the sexes. Fire appears to be the most important natural disaster provocative event with rates of 3.8%.

Vulnerability factors that increase the risk of developing the disorder include a history of psychiatric disorder, particularly anxiety or depression, and also a family history of psychiatric illness (McFarlane, 1989). PTSD is associated with high levels of comorbidity with other psychiatric disorders. The most common current comorbid conditions have been reported to be major depression, followed by generalised anxiety disorder and substance abuse disorders.

Over the last 25 years biological investigation into PTSD has made considerable progress focusing on the HPA axis and on possible regional neuro-anatomic abnormalities involving the limbic system (Hamner et al., 1999; Yehuda, 1998).

Evidence of efficacy must be judged on the basis of placebo-controlled investigations. While claims of efficacy have been made for a number of treatments on the basis of open studies, positive results from placebo-controlled studies are available for only some tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI). Imipramine, desipramine and amitriptyline have all been

reported to have some benefit in treating patients with PTSD but the weight of evidence suggests that their effect is largely on the depressive symptoms. This strengthens the need to take care in controlling for the amount of depression included in PTSD controlled studies. The evidence for the efficacy of SSRIs is more firmly based. Some of the positive studies with SSRIs have been able to control for the presence of major depression better than others. Some depressive symptomatology appears however to be part of PTSD so that it is not easy to examine a population suffering from PTSD without there being some depressive symptomatology present.

Diagnostic criteria

Controlled studies to establish efficacy of treatments for PTSD must use internationally recognised diagnostic criteria. The diagnostic criteria that have been used most frequently in studies come from DSMIII-R (American Psychiatric Association, 1987), which requires re-experiencing of the trauma, avoidance of reminders of the trauma, a numbing of general responsiveness along with increased arousal. In DSMIV (American Psychiatric Association, 1994) clinically significant distress or impairment of functioning, implied in DSMIII-R, was included as a specific criterion for the diagnosis.

There is relatively little difference between DSMIII-R and DSMIV and it is therefore reasonable to assume compatibility between the results using either diagnostic criteria. This view is supported by recent studies (Connor et al., 1999; Davidson et al., 1997a).

The ICD10 diagnostic criteria (World Health Organisation, 1992) are in broad agreement with DSMIV but in ICD10 the criterion for impairment is that the trauma causes pervasive distress rather than clinically significant distress and fewer symptoms of avoidance are required to meet the diagnosis. The prior duration of illness criterion

of at least one month before a diagnosis can be given in DSMIV is less strictly defined in ICD10, which says PTSD may start within a few weeks of a trauma. These differences are thought to account for some of the discrepancies that arise in diagnosis between the two systems (Peters et al., 1999). The research criteria developed for ICD10 have been used in too few efficacy studies to allow any data driven judgement on how well it may serve in future studies.

On the basis of current knowledge the DSM diagnostic system is preferred for use in studies on PTSD.

Establishing a diagnosis

The diagnosis may be established either clinically to determine that the criteria are met or via a structured diagnostic interview. In the studies of PTSD both systems have been used satisfactorily.

The Structured Interview for PTSD (SIP) (Davidson et al., 1997b), which is based on DSMIV, has been used and validated in several studies. The scale covers all the items required for the diagnosis of PTSD scoring them on a present or absent basis and an assessment of severity of symptoms can also be made using the scale.

The Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990) is constructed for two uses: the CAPS-1 was designed as a general diagnostic scale and is able to assess lifetime and current PTSD. It covers what are considered the core symptoms and follows the criteria in DSMIV. The CAPS-2 is used to assess severity at repeated intervals. The CAPS scale is comprehensive but tends to be cumbersome and time consuming to administer. It is possible that the lengthy discussion of trauma and response required might have the effect of providing unassessed behavioural treatment. The use of the CAPS-1 should probably be confined to a screening visit.

A version of the CAPS has been developed for use

Table 1
DSMIV Criteria for posttraumatic stress disorder

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- A. Exposure to a traumatic event that involved actual or threatened death or serious injury or threat to the physical integrity of self or others and the person's response involved intense fear, helplessness, or horror.
 - B. The event is persistently reexperienced through intrusive distressing recollections, images, perceptions, or dreams; or the feeling that the traumatic event is recurring including hallucinations and flashback episodes; or intense distress or physiological reactivity on exposure to internal or external cues to the traumatic event.
 - C. Persistent avoidance of stimuli associated with the trauma and numbing of responsiveness indicated by three of:
 - Avoidance of thoughts, feelings, or conversations associated with the trauma
 - Avoidance of activities, places or people that arouse recollections of trauma
 - Inability to recall an important aspect of the trauma
 - Diminished interest or participation in significant activities
 - Feelings of detachment from others
 - Restricted range of affect
 - Sense of foreshortened future.
 - D. Persistent symptoms of increased arousal shown by two of:
 - Sleep difficulties; irritability; concentration difficulties; hypervigilance; exaggerated startle response.
 - E. Duration is more than 1 month
 - F. Clinically significant distress or impairment
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specifically in children and adolescents. The structured clinical interview covers the same seventeen symptoms given in DSMIV with associated items targeted at children from the age of 8 through early adolescence.

There is some concern that a structured diagnostic interview might miss important information that would be elicited in a careful clinical evaluation of the patient. It is therefore recommended that a thorough clinical exploration should be made before a structured or semi-structured interview is used.

Prior duration of the disorder

A minimum prior duration of illness is an important part of the diagnostic criteria in DSMIII and DSMIV. A minimum duration of one month is required for the acute form of PTSD and 3 months for the chronic form. This constitutes a major difference from ICD10 where a minimum duration is not emphasised, and this is considered to be inappropriate for efficacy studies. The results from efficacy studies point to the need for a minimum duration criterion in order to differentiate PTSD from an acute stress reaction that resolves within a month and to avoid the confounding effect of the high placebo response rate associated with spontaneous resolution of acute stress reactions.

Studies have focused mainly on PTSD that persists for more than three months or, though much less frequently, on PTSD that arises after at least six months. Current evidence suggests that some cases of PTSD resolve spontaneously within three months and that a prior duration of longer than three months is therefore more likely to identify a treatment responsive population with a lower placebo response rate. This is important as experience in other conditions suggests that studies where a high placebo response rate is seen have a much reduced chance of testing for efficacy.

In some instances a population with a mean prior duration of two years has been associated with an even lower placebo response rate. There is no evidence to date suggesting that prior duration identifies separate populations and therefore separate studies in groups with different duration are not needed.

It is sensible to exclude patients with a short prior duration of PTSD, which may be confused with an acute stress reaction. It seems unwise to include patients with a prior duration of less than 6 months (in line with the criteria for GAD) but there are too few data on which to base any further formal recommendations.

Assessment of stressors

To fulfil criteria for PTSD the stressor leading to PTSD has to be perceived as serious, involving actual or threat-

ened death or serious injury to self or others. Therefore, according to DSMIV a mild stressor cannot lead to PTSD and the assessment of the nature and severity of the stressors becomes very important.

For studies of PTSD the nature of the stressor, or stressors since more than one stressor is frequently reported, needs to be identified, and the perceived severity and the duration of exposure should be documented. The severity of the stressor should be judged independently of the symptoms or dissociation that develop. In some patients PTSD develops after some delay and the time from the stressor to the evolution of symptoms should be recorded.

The precipitating stressors vary considerably but the PTSD, once it has developed, does not. There are no data currently to suggest that PTSD differs clinically according to the type of trauma or setting, much as major depression, once it develops, is no longer related to the precipitant. On this basis efficacy found in studies in PTSD following one type of trauma should be applicable to PTSD in other settings. There was a consensus that there should be no requirement for separate studies of PTSD in different settings or with different traumas and the results from studies should be generalisable to the disorder. However, because of the limited data available it may be advisable that the population investigated should not be limited to one trauma or setting.

Patient sample

The population to be investigated in efficacy studies should be precisely defined. Studies have been carried out on a variety of populations drawn from different settings and some variation in the response to treatment has been seen. For example a consistent finding in the USA is that civilian patients show a better response to treatment than veterans recruited from Veteran Affairs Clinics. However efficacy of drug treatment has been demonstrated in both in the USA (Connor et al., 1999) and veterans with PTSD recruited in other countries do seem to respond. It is likely that the difference in level of response observed reflects comorbid alcohol or drug abuse, and/or potential secondary gain.

Response may be affected in cases where financial compensation for trauma is an issue or where the individuals would be expected to incur substantial loss if they responded to treatment. Questions of possible secondary gain should be taken into consideration when selecting the study population.

The evidence indicates that a clearer drug placebo differentiation is seen where PTSD has breached a minimum level of severity. Evidence of efficacy in mild or minimal PTSD is difficult to establish. To establish efficacy it is therefore appropriate to include patients with a minimum level of severity even though this might limit

the generalisability of the results as regards those with the milder conditions. One widely used minimum criterion for severity in studies has been a score of 50 or more on the CAPS2. In efficacy studies in PTSD the basis for selecting the minimum severity criterion for inclusion in the studies must be defended.

There have been few studies specifically in children but PTSD appears to be the same disorder in children as in adults though the expression of symptoms may differ, for example distressing recollections of the event may be identified through repetitive play on the theme of the event. If PTSD is the same condition in children and adults separate studies may not be necessary to demonstrate efficacy but will be needed to establish the dose, safety and pharmacokinetics of the treatment in children. For an indication in children regulators may well demand separate studies.

There is no evidence from the studies carried out in the general population to suggest that PTSD in the elderly differs in any way but additional studies may be necessary to establish the appropriate dose and address the safety issues. The elderly form a more difficult population for medication treatment studies because of the changed pharmacokinetics, the increase in comorbid medical conditions and the consequent likelihood of concomitant treatment, and possible differences in pharmacodynamics.

Comorbidity

The influence of various comorbid psychiatric conditions needs to be considered when undertaking studies to establish the efficacy of treatment in PTSD. Studies should be able to establish a specific anti-PTSD effect independent of possible therapeutic benefit secondary to effects on complicating comorbid conditions.

Comorbid depression, which is common, poses a particular problem since it may itself be precipitated by the same stressor that provoked PTSD and it may also be a precursor for the development of PTSD. The core symptoms of PTSD include some depressive symptoms and are associated with functional impairment. Moreover, a number of potential treatments under investigation for PTSD are established antidepressants, or are being investigated as antidepressants. The presence of comorbid major depression complicates the interpretation of results and the assessment of the extent to which there is a direct effect on the PTSD.

Attempts have been made to separate the effects of treatment on PTSD and depression by estimating the covariate response rates or by using path analytic techniques. Regulatory authorities may not consider these sufficient in pivotal studies. Another method has been the exclusion of those individuals with a prior history of major depression before the trauma or those with current depressive symptoms of a severity that would be expected to

respond to an antidepressant and which would therefore complicate the interpretation of the effect on the PTSD. Similar restrictions on the permitted level of severity of comorbid depressive symptoms have been applied in pivotal placebo-controlled studies in OCD, panic disorder, and social phobia where comorbid depressive symptoms have presented a similar methodological problem.

It seems appropriate to recommend for studies in PTSD that primary DSMIV major depression should be excluded. It is also appropriate to recommend the method used in studying other anxiety disorders: that permitted secondary symptoms of depression should not be of a severity where antidepressant response is expected. In studies of PTSD the maximum level of permitted depressive symptoms, defined on depression severity scales, needs to be justified and the way major depression and other comorbidity is diagnosed should be documented.

There is also evidence that some of the treatments being investigated in PTSD are effective, or are thought to be effective, in other disorders such as OCD, panic disorder, social phobia and GAD. It is important to determine whether or not patients have a diagnosis of these disorders prior to the development of PTSD in order to establish a direct and independent effect of the treatment on the PTSD. The severity of secondary symptoms of comorbid conditions should be kept at a mild level and the maximum permitted severity justified as being unlikely to have undue influence on the results in PTSD.

Severity scales

The severity scales used to measure the severity of PTSD in efficacy studies need to be internationally recognised, to be validated before the study to measure the severity, and to be sensitive to change with treatment. The choice of pivotal scales for assessing efficacy should be identified a priori as in studies in other conditions.

The scales differ in sensitivity to treatment effects and this will affect the power calculations in determining the required size of the study. A number of severity scales have been used to measure response in placebo-controlled studies. These include the clinician rated TOP 8 (Davidson and Colket, 1997), the CAPS 2 (Blake et al., 1990), and the Duke Global Rating Scale for PTSD (Davidson et al., 1998). Self-rated instruments include the Impact of Events scale (IES) (Horowitz et al., 1997), the Davidson trauma scale (DTS) (Davidson et al., 1997c), and the PTSD Checklist (PCL).

Scales for assessment of severity should cover the core symptoms. The TOP-8, which was developed from the structured interview SIP, was specifically designed as a brief scale for the assessment of treatment outcome. It comprises eight items each measured on a scale of 0–4 with defined anchors given for each item and the scale combines severity and frequency. The items cover the four

core features of intrusion, avoidance, numbing and hyperarousal. The scale has been shown to have good psychometric properties and to correlate well with other independent measures of severity. The TOP-8 has been shown to be useful in placebo-controlled studies (Connor et al., 1999).

The CAPS-2 is designed for repeated use using the items of the CAPS-1 to rate the symptoms of PTSD in the previous week. It measures 17 symptoms of PTSD some of which are less common and thought to be less sensitive to changes in severity. It is time-consuming to administer and repeated administration may provide an element of behavioural therapy. The CAPS-2 has been used in a number of placebo-controlled studies and has been able to distinguish drug from placebo effects. Both the TOP-8 and the CAPS-2 scales are regarded as suitable for efficacy studies.

The IES (Horowitz et al., 1997) is a self rated scale based on a list of items drawn from common experiences of intrusion and avoidance. The scale has been found in some populations to be able to find a significant drug placebo difference and provides some independent patient-driven measure of efficacy. The DTS (Davidson et al., 1997a) is a 17 item scale following the DSM-IV criteria which the subject completes with a rating of severity and frequency. It has been used successfully to detect significant differences in placebo-controlled studies.

The difference in sensitivity and the possible increase in placebo response associated with the repeated use of some scales such as the CAPS 2 needs to be taken into account in calculating the sample size needed to test efficacy.

A good treatment for PTSD should have effects across the spectrum of PTSD symptom clusters. With effective treatments efficacy across these clusters measured on the most frequently used pivotal scales is generally seen to covary. Separate placebo-controlled demonstration of efficacy on the four core symptom clusters individually is not required.

Dose

The recommended dose for treatment for PTSD needs to be justified. The usual design in other anxiety disorders as well as depression is to compare the efficacy of preferably three fixed doses compared to placebo. An initial titration period at the start of the study is normally used to avoid an abrupt challenge with high doses of the drug.

Control groups

To establish efficacy, double blind placebo-controlled studies are necessary. At the moment, no treatment for PTSD is licensed in the EU. It is therefore difficult to argue for a comparator anti-PTSD treatment as a reference

control and three way studies at this point would be difficult to defend. The usual requirement of a minimum of two positive placebo controlled studies is obviously necessary, one of which may be a long-term study. Where there is agreement about a reference treatment three-way studies would be preferred. For long-term efficacy where so few data are available, a placebo control is obviously necessary.

Clinically relevant changes

In Europe it is usual to establish not merely that the treatment is better than placebo on the pivotal severity scale but also that the change seen is clinically relevant. Several definitions of clinical relevance have been used in studies of other conditions turning to independent measures such as a responder analysis or differential effects on disability. One definition has been the treatment effect in the responder analysis with a significant difference in the number of responders. It is important that the study should be sufficiently large to be able to detect a significant difference in the responder analysis.

Percentage change scores of 35%, 40% and 50% have been used on both the TOP-8 and the CAPS 2 as a definition of responders. The most appropriate level of percentage response is approximately at the midpoint between the response on placebo and the pharmacological response. This level will vary with the responsiveness of the population studied. With the TOP-8 there is little difference between these criteria so that the 50% reduction of the total score on the pivotal scale that is commonly used in other disorders has a certain validity. For the CAPS-2, which is less sensitive, the lower percentage improvement scores might be more appropriate.

If percentage change is used as a responder criterion it is important to take into account the severity of PTSD in the population studied when choosing the appropriate level. For example, in a treatment resistant population where achieving a response is likely to be more difficult a lower percentage change might be expected to be more relevant to define responders. As with other conditions the definition of responder needs to be specified *a priori* in the study.

The clinician's global assessment provides a measure of overall response separate from the scale scores but the assessment needs to be specific to the disorder. The Duke Global Rating scale has been used to establish efficacy by a global judgement of the investigator. The Global Score measure of 1 or 2 (no symptoms or minimally ill) has been used as a clinically relevant measure of response but in some studies the Global Score of 1 (no symptoms) has turned out to have a larger drug placebo difference (Connor et al., 1999).

Other measures of disability have been used such as the self-rated Sheehan Disability Scale (Sheehan, 1996) which provides a measure of disruption in work life, social life,

and family life. This type of scale has been able to reflect reliably a difference between drug and placebo and may be used as an independent secondary measure of disability. It may also help in defining a responder on the more specific scales.

Duration of short term studies

The duration of placebo-controlled studies of PTSD needs to be sufficiently long to establish clear-cut efficacy. If the study period is too long there is an increased risk of attrition which may weaken the validity of the study. Acute treatment studies that have had positive results in PTSD have varied in length between 8 weeks and 12 weeks depending on the sensitivity of the methodology, the treatment responsiveness of the population studied, and the relative lack of placebo response. Some of the most recent large multi-centre studies have been able to establish efficacy by 8 or 10 weeks (Connor et al., 1999; Davidson and Farfel, 1999).

There are insufficient data based on controlled treatment studies to make definitive recommendations on the length of study. The current status suggests that short term studies need to have a duration of around 12 weeks though this figure may need to be revised down as data from further studies become available. It is therefore recommended that placebo-controlled studies of short-term treatment should have a duration of 10 to 12 weeks.

Duration of long-term studies

PTSD is often a chronic, long-term disorder with patients suffering from the disorder for many years. In Europe, the Committee for Proprietary Medicinal Products (CMP) recommends that long-term efficacy is established separately in chronic disorders where treatment is likely to continue over the longer term. Studies will therefore be needed to establish that the treatments are not merely effective in acute treatment but that they continue to be effective in long-term treatment.

There are few long-term data currently available on the efficacy of long-term treatment in PTSD. There are sufficient data to show that long-term treatment is associated with better outcome and lower levels of disability (Davidson, 2000) and it would seem that the clinical practice of providing long-term treatment is justified. Following the requirements for other similar anxiety disorders it is reasonable to require controlled evidence of persistent efficacy of the treatment for a period of 6 months. Evidence of long-term efficacy is obtained from two types of studies: treatment extension and treatment discontinuation. Data from blinded extension studies where responders on active treatment or placebo are continued for a further 6 months have been used successfully in depression (Com-

mittee for Proprietary Medicinal Products, 1994). However, in these studies the size of the groups is likely to be unequal and there may be some difficulty interpreting the results. The alternative design, which is preferred, is the randomised withdrawal study. In these studies responders to active treatment are rerandomised to receive the experimental treatment or placebo and the number of relapses and time to relapse are compared using survival analytic techniques. Abrupt treatment discontinuation effects could possibly compromise these studies and the appropriate taper period should be included before the placebo period.

Conclusion

PTSD is a common, serious disorder that is a clear public health problem (Solomon and Davidson, 1997). Established effective treatments for PTSD are clearly needed. Efficacy of potential treatments needs to be shown compared to placebo both in short and long term studies and safety of treatment needs to be established. Treatments for PTSD needs to show efficacy independently of possible direct antidepressant effects which may be difficult since PTSD itself encompasses some depressive symptoms. Studies that use the methodology outlined in this report should have a good chance of being able to assess direct treatment effects.

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