Pharmacological and Behavioural Treatment of Panic Disorder

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Drug studies of panic disorder (PD) have involved tricyclic antidepressants, monoamine oxidase inhibitors, beta blockers, and benzodiazepines. Among benzodiazepines, alprazolam has received wide attention in recent years. The results of the Cross-National Collaborative Panic Study (CNCPS), the largest study of alprazolam (and imipramine) in PD, involving more than 1,600 patients, have recently become available. A review of the recent evidence concerning the value of drugs in PD is thus timely.

Earlier claims of a selective imipramine effect on panics were not confirmed by later studies showing that tricyclic antidepressants and benzodiazepines affect both anticipatory anxiety and panics when given at sufficient doses. Studies of the effect of adding imipramine to exposure [1-3] found no additional benefit at follow-up. Results from studies of monoamine oxidase inhibitors and beta blockers have not been more encouraging than the results of studies of imipramine.

Two placebo-controlled studies of alprazolam (CNCPS) – phase I [4] (alprazolam in 481 patients with PD) and phase II [5] (alprazolam or imipramine in 1,168 patients with PD) -have recently been published. Although both studies claimed superiority of alprazolam over placebo, their methodological problems do not appear to justify this conclusion [6]. Both studies had an unacceptably high dropout rate in the placebo group (46 % in phase I and 44% in phase II) which led to problems in the analysis of the data. In both studies two sets of results were reported, one based on completer and the other on end point analyses at week 8. The latter were based on scores imputed from the last ratings available which often meant carrying over scores from week 4 to week 8 for placebo dropouts. In phase I alprazolam was better than placebo in most measures in end point analyses, but only in 4 out of 21 measures in completer analyses. In phase II a significant alprazolam effect was found in 5 out of 24 measures in end point analyses and in only one measure in completer analyses. The effect of alprazolam was thus impressive only in the end point analyses in phase I, but not in phase II; it was negligible in completer analyses in both studies.

In both studies end point imputation was based on the assumption that early placebo dropouts were non-responders who would not have improved had they remained in the trial until week 8. This assumption is difficult to justify and may well be mistaken. In another study on alprazolam and exposure in PD with agoraphobia [Marks et al, unpubl. data], the placebo group which had a dropout rate of only 13 % continued to improve on panic measures until week 8. The dropouts were less ill on their ratings at the time of termination of treatment than were completers. Thus, dropping out from treatment may not necessarily be due...
to a lack of response to treatment. Neither the phase I nor the phase II study compared early dropouts with completers at the time they dropped out from treatment.

Most drug studies of PD, including the CNCPS, did not have a psychological treatment component or a discontinuation and drug-free follow-up phase in their design. A comparison of alprazolam with behavioural treatment would be desirable, since the latter is known to be effective in PD with agoraphobia. A drug trial should also include a discontinuation and follow-up phase, since agoraphobia is a chronic anxiety disorder.

The recent trial of alprazolam in PD [Marks et al, unpubl. data], conducted in London and Toronto, included both an exposure component and a treatment-free follow-up phase. 154 patients with PD and agoraphobia received either alprazolam or placebo, combined with either exposure or relaxation (a psychological placebo). Unlike in phases I and II, the treatment groups did not significantly differ in early dropout rates (13% in the placebo group). At the end of treatment the exposure effect was twice the alprazolam effect on most measures. The drug effect was lost on all measures after stopping the medication. Exposure effects, however, were maintained at post-taper and at 10 months of follow-up. Survival analyses indicated a greater risk of relapse in exposure patients treated with alprazolam. The best long-term results were thus achieved by exposure-only treatment. A strong placebo response was noted on all panic measures, no treatment being superior to placebo in reducing panics.

The claims of a specific antipanic effect for alprazolam (or imipramine) do not appear to be supported by the results of the CNCPS. In both phases I and II the drug effect on panic was significant only on end point and not on completer analyses. In a study of phase II patients [7] alprazolam and also imipramine had a significant effect on phobia and global improvement measures only in patients with PD with agoraphobia, not in patients with uncomplicated panic or limited avoidance.

The drug effect on panic in the agoraphobic group was weak and barely significant (p < 0.05), and then only in end point analyses. In patients with no agoraphobia neither drug reduced panic significantly. The authors concluded that the drug effects were mediated through avoidance behaviour.

In the London/Toronto study neither alprazolam nor exposure had a significant effect on any of the panic measures due to a strong placebo response in panic. Post-treatment global improvement as rated by both clinicians and patients was strongly related to improvement in agoraphobic avoidance and not to remission in panic. Many severe agoraphobics had merely one or two panics a week which remitted in some cases without loss of agoraphobic disability. Patients often reported more satisfaction with being free of travel restrictions than with being panic free, even though travel freedom meant having to face panic.

These findings question the value of panic as a primary criterion of treatment outcome. They also have important implications for clinical practice. When faced with patients who have both panic and some agoraphobic avoidance (the majority of PD cases), a clinician has to decide which to target in treatment. In most treatment studies of PD panic fluctuated hugely with a variance greater than the mean, and panic improved easily even with placebo. It was reduction in agoraphobic disability that related to global improvement.
Side effects of drugs can be a problem in treatment. In the London/Toronto study alprazolam patients reported significantly severer sedation, fatigue, irritability, memory problems, impaired mentation, ataxia, slurred speech, appetite decrease, and weight loss than did placebo patients. Other well-known problems with long-term benzodiazepine use include decreasing effectiveness, increasing tolerance, dependence, with withdrawal symptoms, and relapse upon withdrawal [8]. Dependence can be a particularly serious problem. In the phase II study 22% of the alprazolam patients versus 8% of the imipramine and 6% of placebo patients continued medication after the study ended.

Another problem with drugs concerns their adverse interactions with psychological treatment. State-dependent learning, though not demonstrated in clinical trials, may prevent transfer of learning during psychological treatment to a non-drug state. Drugs may also interfere with learning by facilitating attribution of treatment gains to medication rather than to one’s own personal efforts. This common clinical observation was tested in the London/Toronto study: alprazolam-treated patients, in comparison to placebo-treated patients, had stronger beliefs that their improvement was due to tablets rather than to psychological treatment. Patients who attributed their gains to medication during treatment did significantly worse at post-taper than those who believed their improvement was a result of their personal efforts during psychological treatment.

In conclusion, drugs in PD confer little benefit which disappears on discontinuation. Exposure-based treatments, on the other hand, can achieve a lasting improvement in PD and agoraphobia.

References