Pharmacotherapy of Anxiety Disorders

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ANXIETY AND RELATED DISORDERS

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Over the past two decades, research interest in the pharmacologic treatment of anxiety disorders has grown enormously. Research and theorizing about the biological bases of anxiety disorders have developed in parallel with pharmacologic studies. Adrenergic hyperactivity has been suggested as an important factor in mediating panic disorder (PD), posttraumatic stress disorder (PTSD), and social phobia (SP); dysfunction in serotonergic systems has been seen as important in obsessive-compulsive disorder (OCD), and regulation of the GABAergic system has been the focus of theorizing about generalized anxiety disorder (GAD). Other biological theories have dealt with disordered respiratory physiology in PD, and dysfunction of endogenous opioid systems in PTSD.

While there is not yet any definitive evidence in favor of a biological etiology for any anxiety disorder, it is clear that these conditions are usually highly responsive to medication. This chapter summarizes current knowledge about the use and efficacy of psychotropic medications in GAD, PD, PTSD, OCD, SP, and agoraphobia.

GENERALIZED ANXIETY DISORDER

Benzodiazepines

Benzodiazepines have been the most widely used treatment for generalized anxiety over the past two decades, having almost completely replaced barbiturates and meprobamate. The majority of controlled comparisons have demonstrated greater anxiolytic efficacy of benzodiazepines than barbiturates, and to a lesser extent, meprobamate (Shader & Greenblatt, 1974). However, the major advantages of benzodiazepines are their much greater margin of safety, their ability to control anxiety without excessive sedation, and their generally (although not invariably) milder withdrawal effects.

Rates of effectiveness of benzodiazepines have been difficult to specify exactly. Rickels (1978) found an overall response rate of about 75%, which may be compared to the 30% average placebo response described by Shader and Greenblatt (1974). However, both drug and placebo responses have varied widely across studies.

Variability of benzodiazepine response is due both to methodological differences and to the heterogeneity of patients treated for generalized anxiety. A great many nonpharmacologic factors have been found to affect patients' acute response to benzodiazepines (Rickels 1978). Better response

has been found in women, those who are employed, those who have higher socioeconomic status, those who see their problems as emotional (rather than due to physical disease), and those who expect medication to help them. Patients with severe anxiety, especially if it is of acute duration, those without concurrent physical illness, and those who have responded well to prior anxiolytic treatment or had no prior treatment, tend to respond best. Physicians' warmth and optimism about the treatment have been found to enhance both medication and placebo responses (Rickels et al. 1970), while ongoing unfavorable life events during treatment diminish response. The lesson of these findings is that patient's social and psychological problems, and the attention the doctor pays to them, may affect the course of generalized anxiety as much as the way in which medication is prescribed.

While patients with generalized anxiety often present with a mixture of symptoms, benzodiazepines do not address them all equally. Rickels (1978) found that drug-placebo differences are due mainly to improvement on HSCL anxiety and somatization factors, with relatively little contribution from depression, obsessive-compulsive, or interpersonal sensitivity factors.

Parameters of dosing and response vary widely among patients. Published studies have generally used the equivalent of 10 to 40 mg diazepam daily, most often in three divided doses. Marked response can often be seen during the first week of treatment, and may even occur within a few

days. While patients may continue to improve through the first several weeks of treatment, response generally plateaus by the end of the fourth week (Rickels, Schweizer, Csanolosi, Case, & Chung, 1988). Downing and Rickels (1985) found that patients who responded to diazepam most robustly during the first week of treatment showed the best outcome after six weeks.

Very little systematic work has been done on long-term treatment with these medications. Many clinicians have been reluctant to prescribe benzodiazepines chronically for fear that patients would habituate to the therapeutic effects, require escalating doses, remain tied to the medication due to withdrawal symptoms, or even develop addictive behaviors that did not exist previously. The few systematic studies of long-term benzodiazepine used to date have not supported these concerns.

While transient withdrawal syndromes on cessation of benzodiazepines are common, Rickels and colleagues (Rickels, Case, Downing, & Winokur, 1983) found that patients taking such medications for longer than eight months were more likely to experience clinically significant withdrawals. Withdrawal effects are more pronounced with abrupt than with gradual withdrawal, and with short-acting rather than long-acting drugs. However, a significant number of patients will have difficulty remaining off medication due to withdrawal effects, even with long-acting benzodiazepines and gradual tapering.

Studies comparing benzodiazepines have found no consistent evidence that some are more efficacious than others. Therapeutic choices are therefore made on the basis of the drug's profile of potency, half-life, and degree of sedation. Patients vary widely in the dose of benzodiazepines they require and tolerate. A typical dosing recommendation would be to start at 2 mg t.i.d. of diazepam, 5 to 10 mg t.i.d. of chlordiazepoxide, or 0.5 mg t.i.d. of alprazolam, and titrate doses upward as necessary, to a maximum dose of 40 mg daily diazepam equivalent.

Tricyclic Antidepressants

The older literature comparing doxepin to benzodiazepines suggested a possible role for this tricylcic in anxious patients with or without some degree of concurrent depression. More recently, amitriptyline, desipramine, and imipramine have been compared to placebo and/or benzodiazepines in double-blind studies, most but not all of which have found them superior for treatment of generalized anxiety. It is difficult to know how to interpret these results, since only two of the studies (Kahn et al., 1986; Hoehn-Saric, McLeod, & Zimmerli, 1988) used current, specific diagnostic classifications, or attempted to factor out the effects of depression or panic-type anxiety on medication response. It is not clear whether the efficacy of tricyclics is due to their well-known antidepressant or antipanic effects, or to alleviation of generalized anxiety itself.

In their double-blind study, Kahn et al. compared 150 to 200 mg daily of imipramine with 60 to 80 mg chlordiazepoxide over an eight-week period. They analyzed separately patients who were primarily anxious, those who were primarily depressed, and those who had anxiety of the panic type. In the primarily anxious group, whether or not there were panic attacks, chlordiazepoxide was more effective than imipramine in improving sleep and anxiety early in the trial, while imipramine was superior to chlordiazepoxide in treating depression and anxiety later in the trial. This study, therefore, suggests a direct effect of imipramine on generalized anxiety.

In the only study to date using DSM-III criteria, Hoehn-Saric et al. (1988) compared imipramine and alprazolam in patients who met criteria for GAD, but not major depression. After a six-week trial, imipramine was superior in alleviating psychological symptoms of anxiety, obsessive-compulsive symptoms, interpersonal sensitivity, paranoia, and depression, while alprazolam was better in alleviating somatic symptoms of anxiety.

In most studies, tricyclics have shown increasing advantages over benzodiazepines as the four- to eight-week study periods progress. This may be due to the general tendency of tricyclic side effects to diminish, and therapeutic effects to increase over the first several weeks of treatment. On average, controlled studies have reported a 42% dropout rate on tricyclics, which seems somewhat higher than the 26% average benzodiazepine rate,

but probably not much different from the 35% dropout on placebo.

Buspirone

Buspirone, a drug of the azapirone class with serotonergic inhibitory effects, is the first approved new medication type for generalized anxiety since the advent of benzodiazepines. Clinical interest in buspirone stems from its very different side effect profile from benzodiazepine anxiolytics. It does not tend to cause fatigue or sedation, does not interfere with psychomotor performance, does not interact with CNS depressants, such as alcohol, and does not produce a withdrawal syndrome when abruptly withdrawn. Like benzodiazepines, buspirone has a very high margin of safety; unlike them, it appears to have no anticonvulsant, muscle-relaxant, or euphoriant effects.

Buspirone has been compared to diazepam, clorazepate, alprazolam, lorazepam, and oxazepam, as well as to placebo in many double-blind trials. These trials have consistently demonstrated its superiority to placebo, and overall equivalence to benzodiazepines (Rickels, 1990). Doses in these studies have typically ranged from 15 to 40 mg daily, given on a t.i.d. schedule. While some studies have found clinically significant anxiolytic effects of buspirone after one week of treatment, its efficacy generally lags behind that of benzodiazepines for the first two to four weeks.

Common side effects of buspirone include nausea, dizziness, headache,

or, paradoxically, symptoms related to increased arousal and tension, especially early in treatment. These side effects seem to be less well tolerated than those of benzodiazepines, since many investigators have reported a higher dropout rate on buspirone in clinical studies, especially among those patients who have previously received benzodiazepine treatment. Patients who have come to expect a rapid onset of action from benzodiazepines may have a particularly hard time tolerating the slower onset of buspirone, although a physiologic explanation for the poorer results in this subgroup has not been ruled out.

Most studies of buspirone have been no longer than four to six weeks. However, Rickels and colleagues (Rickels & Schweizer, 1990) have conducted a six-month maintenance study on a group of patients who were then followed for up to 40 months. At the end of six months, efficacy of buspirone was equivalent to that of clorazepate, with no evidence of loss of efficacy of either drug over time. Upon double-blind withdrawal of medications, withdrawal and rebound symptoms were evident in clorazepate, but not in buspirone users. At both six and 40 months of follow-up, patients on buspirone were significantly less likely to have moderate or severe anxiety, or to be using anxiolytics, than those who had taken clorazepate. These data suggest that buspirone may produce longer lasting effects than benzodiazepines, a possibility that will have to be confirmed in future studies.

Other Agents

Because of their ability to decrease adrenergic activity, beta-adrenergic blocking agents have been viewed as potential anxiolytics. Hayes and Schulz (1987) recently reviewed the results of double-blind studies of beta blockers for generalized anxiety, eight using propranolol and five using other agents. The authors concluded that while beta-blockers tend to be more effective than placebo, they are usually less effective than benzodiazepines. While earlier workers suggested that beta-blockers might be more effective in alleviating the somatic rather than psychological aspects of anxiety, this has not been confirmed in more recent work (Meibach, Donner, Wilson, Ishiki, & Dager, 1987).

Since their introduction, phenothiazines have been known to have anxiolytic properties in nonpsychotic as well as psychotic patients. This has been demonstrated in several controlled studies comparing neuroleptics to placebo (Mendels et al., 1986). However, there have been no controlled studies comparing neuroleptics to other anxiolytics in nonpsychotic patients. Since the risks of both acute and chronic extrapyramidal side effects are obvious liabilities of neuroleptics, their use could not be recommended without data suggesting specific indications or advantages over more commonly used anxiolytics.

PANIC DISORDER AND AGORAPHOBIA

Tricyclic Antidepressants

Imipramine is the drug most systematically studied for treatment of panic and agoraphobia. Of 13 studies in which imipramine has been compared to placebo under double-blind conditions, 10 have clearly demonstrated the drug's efficacy. Imipramine's antipanic effects have been found to be separate and independent from its antidepressant effects. Some investigators have found primary antipanic and secondary anti-avoidant effects while others have found the reverse.

The efficacy of imipramine without concurrent behavioral therapy has been somewhat less convincingly demonstrated than the benefit of adding imipramine to such therapies. While simple exposure instructions may be effective as adjuncts to medication, patients who are encouraged to continue avoiding phobic situations seem not to do well on medication.

The average dose of imipramine reported in controlled studies is about 160 mg daily, which is comparable to the usual minimum antidepressant dose in nongeriatric adults. There is evidence that patients at times respond more poorly at doses substantially above or below this level (Ballenger et al., 1984). Furthermore, some patients seem to get good therapeutic responses at very small doses, at times as low as 10 or 15 mg daily (Jobson et al., 1978). There

have been few studies of blood levels in relation to therapeutic effects, and the results of those have been inconsistent.

The range of response rates in published reports is 60 to 80%, with a mean of about 78% substantially improved on medication. Most, though not all of these rates, have been measured in terms of efficacy of antipanic effects. By comparison, the range of reported placebo responses is 33 to 72%, with a mean of 51%. Thus, a great many potentially medication-responsive patients may do equally well on placebo (Mavissakalian, 1987).

Time of onset of antipanic action is generally two to four weeks. However, some authors have reported continued improvement as far as five or six months into treatment, so that maximum benefit may require a fairly lengthy trial (Zitrin et al., 1983). A major factor effecting time of onset is the difficulty in getting patients up to a therapeutic dose because of poorly tolerated side effects. In addition to the usual anticholinergic and hypotensive effects, panic patients appear to be especially prone to "amphetamine-like" effects of imipramine, including feelings of increased anxiety, energy, tension, restlessness, or shakiness, with or without concomitant palpitations, diaphoresis, tremulousness, and sleep disturbance.

There is general agreement that substantial numbers of patients will relapse when taken off medication, but there is little systematic data

available. Published reports cite relapse rates of 20 to 50% following medication withdrawal, but the studies vary as to length of follow-up and amount of concurrent behavior therapy.

At present, the literature offers few predictors of imipramine response. Long duration of illness, increased severity, prominent depressive symptoms, relative lack of panic attacks, and predominance of simple phobia have all been associated with poorer outcome (Sheehan et al., 1980; Mavissakalian & Michelson, 1986). Recently, personality pathology has been associated with poorer global outcome, but not with antipanic effects of medication.

There is no reason to think that imipramine is unique in its antipanic efficacy among cyclic antidepressants. Controlled studies have demonstrated similar efficacy of clomipramine and zimelidine, and uncontrolled trials and anecdotal reports have suggested the efficacy of desipramine, amitriptyline, and nortriptyline. Clinical experience confirms the utility of these and other cyclic antidepressants in treating panic attacks.

Monoamine Oxidase Inhibitors

The antipanic effect of MAO inhibitors has been less thoroughly studied than that of imipramine and other cyclic antidepressants. The literature contains six controlled studies (five dealing with phenelzine) and a number of uncontrolled clinical trials. Methodological inadequacies notwithstanding, all

published reports have found some type of anxiolytic effect for MAOIs, with an average response rate of about 80%. A study by Sheehan et al. (1980) provides the only controlled comparison of phenelzine and imipramine, showing a trend toward superiority of the former drug on most measures of improvement. The range of target symptoms affected by MAO inhibitors is very similar to those of cyclic antidepressants.

Doses of phenelzine have been reported in the range of 30 to 90 mg daily, but most studies have not used more than 45 mg, which may be under the optimal level. There is, as yet, no published data on the relationship of platelet MAO activity to therapeutic effect.

Time of improvement ranges from three to eight weeks of treatment, with a mean of about four weeks. About 20% of patients fail to complete treatment across studies, suggesting that MAOIs may be somewhat better tolerated by panic-agoraphobic patients than cyclic antidepressants.

At present there is little guidance for predicting which patients will respond to MAOIs, or which drug within the class may be most effective. Level of depression, personality pathology, and duration of illness have been associated with poorer outcome in some, but not all studies.

Fluoxetine

In addition to its antidepressant and antiobsessional effects, fluoxetine appears to be an effective antipanic agent in a few reports published to date. Schneier et al. (1990) reviewed the charts of 25 patients who had received open trails of fluoxetine for panic disorder, and found improvement in 76%. The dose range was 2.5 to 80 mg daily, and the dropout rate was 16%. The authors noted that many patients needed to start on as little as 2.5 mg daily, with no more than weekly increments, in order to tolerate the treatment. The main difficulty is the early side effects which may include jitteriness, agitation, decreased sleep, and gastrointestinal disturbance. On the other hand, anticholinergic effects and weight gain are generally absent with fluoxetine.

Benzodiazepines

Although Klein (1964) suggested in early reports that benzodiazepine-type anxiolytics were ineffective for panic attacks, interest in possible antipanic properties of these medications has revived considerably in the past decade. The major focus of attention has been on the triazolobenzo-diazepine, alprazolam (Ballenger et al., 1988) although this compound is not unique among benzodiazepines in its antipanic effects.

Of 10 controlled studies of alprazolam in panic disorder all have shown the effectiveness of the drug, with a mean response rate of about 72%

compared to a placebo response ranging from 14 to 63%. Alprazolam has been found to reduce both spontaneous and situational panic attacks, as well as anticipatory anxiety.

Daily doses of alprazolam have ranged from 1 to 10 milligrams, with a mean of 3.7 mg. Although carefully designed studies of dose response have not been done, some authors have suggested that 40% or more of patients may need 4 to 10 milligrams daily for a good response. Alexander and Alexander (1986) obtained good antipanic effects at a mean dose of 2.2 mg, but needed an average of 3.9 mg for substantial improvement of phobic avoidance.

Alprazolam appears to be both faster in onset and better tolerated than antidepressants. Virtually all reports have described a clinically significant response in one week or less, although continued improvement has been found after six or seven weeks of treatment. Alprazolam is the only antipanic drug so far studied for which the placebo dropout rate (28% in three studies) exceeds the dropout on active drug (12% in six studies).

The most common concerns about alprazolam and other benzodiazepines are the possibility of habituation to therapeutic effects, and the risk of rebound/withdrawal syndromes when the dose is lowered. While many patients may require an increase over their initial therapeutic dose

early in treatment, follow-up studies of up to four years have demonstrated that doses of benzodiazepines tend to remain stable or decrease over time (Davidson et al., 1990). Thus, there is little evidence that patients become habituated to therapeutic effects, or escalate dosage inappropriately.

Recent controlled studies of benzodiazepines other than alprazolam, including diazepam, lorazepam, and clonazepam, suggest that they too are effective antipanic agents. Clonazepam, a high-potency benzodiazepine with a half life of 18 to 54 hours (as compared to 8 to 14 hours for alprazolam) has received particular attention because its longer half-life mitigates interdose rebound/withdrawal effects and attendant anticipatory anxiety. Herman et al., (1987) found that most patients were able to use a twice daily dosing schedule on clonazepam, whereas they had required four or more daily doses when taking alprazolam.

POST-TRAUMATIC STRESS DISORDER

Monoamine Oxidase Inhibitors

Because of their history of use in patients with highly anxious depressions, MAO inhibitors have been logical choices for treatment trials in PTSD. While many anecdotal reports and uncontrolled trials have been published, there have been only two controlled studies of MAOIs to date.

Outcomes in these reports have been quite variable. In the controlled studies, Frank, Kosten, Giller, and Dan (1988) found that 64% of patients improved on phenelzine compared to only 27% on placebo, while Shestatzky, Greenberg, and Lerner (1988) found no significant difference between phenelzine and placebo, although a trend favored the former. In two open trials, the overall response rate averaged about 78% showing at least moderate improvement. The number of patients in these studies is quite small, ranging from 10 in the smallest study to 34 in the largest.

Improved sleep, decreased nightmares, and decreased intrusive daytime recollections have been the most commonly reported benefits among patients who improve on MAO inhibitors. Most authors have reported decreased flashbacks as well, although some have noted that flashbacks may worsen on these medications. Thus, when they are effective, MAO inhibitors appear to ameliorate some of the core symptoms of PTSD independent of their effect on depression and anxiety. These latter symptoms have been reported to improve markedly by some authors and relatively little by others. Avoidance of thoughts, feelings, activities, or situations associated with the trauma is unlikely to be affected by MAO inhibitors in these reports. A number of authors comment on the positive interaction between these medications and psychotherapy.

Medication doses range from 30 to 90 mg daily; only two investigators

measured platelet MAO levels, both at greater than 80% inhibition, and both reporting positive results. While some reports describe almost immediate improvement in some patients, others suggest a need to treat for at least six to eight weeks to attain maximum improvement. In most published reports, patients have been followed for no more than a few months, and there are as yet no systematic long-term studies of PTSD patients on MAO inhibitors.

It is not clear from the currently available literature why treatment response is so variable, nor have any predictors of response yet emerged. The group reporting the poorest therapeutic response to MAO inhibitors (as well as to other antidepressants) describes a patient population with much lower rates of substance abuse and antisocial behaviors than most published studies. It is not apparent why this should predispose to poor medication response, however.

Tricyclic Antidepressant

The status of our knowledge about tricyclic antidepressants for PTSD, and the general pattern of results with these medications are quite comparable to those with MAO inhibitors. The literature contains three controlled, double-blind studies of tricyclics, five open studies or systematic chart reviews, and a number of unsystematic or anecdotal reports. While all studies reported evidence of improvement on tricyclics, the proportion of

patients improved has been quite variable, and the improvement is frequently of modest degree. Among the controlled studies, improvement rates (along various dimensions) range from 27 to 75%, while placebo responses range from 11 to 27% (Frank et al., 1988; Reist et al., 1989; Davidson et al., 1990). Among uncontrolled studies in which improvement rates are reported, from 68 to 100% of patients were reported to be better on some dimension after tricyclic treatment.

The response profile with tricyclics has been quite similar to that with MAO inhibitors. Insomnia, nightmares, intrusive recollections, hypervigilence, and autonomic arousal generally improve, while affective blunting and avoidance generally do not. The relationship between improvement in PTSD core symptoms and improvement in depression or anxiety has been quite variable. Reported doses of tricyclics have been comparable to antidepressant doses, ranging from 50 to 350 mg daily (imipramine equivalents), and averaging in the 150 to 300 mg range. Blood levels have been reported to correlate with improvement in depression in one study using desipramine (mean level 107.3 mg/ml, Reist et al., 1989), but to be unrelated to response in another which employed amitriptyline (Davidson et al., 1990). Length of treatment has ranged from three to eight weeks. While some investigators have described almost immediate improvement, others have found a lag time, with significantly greater response at eight than at four weeks. In the only long-term follow-up of PTSD patients on tricyclics, 9 of 12 Cambodian

refugees were symptomatically improved after 12 months on dimensions of sleep and hypervigilence, but only 5 no longer met criteria for the disorder.

Among the tricyclics used for PTSD have been amitriptyline, imipramine, desipramine, and doxepin. In the only direct, double-blind, controlled comparison of antidepressants, imipramine and phenelzine were both significantly better than placebo, although phenelzine appeared slightly more effective in relieving core symptoms of nightmares, flashbacks, and intrusive memories (Frank et al., 1988). Some authors have suggested that amitriptyline may be more effective than other tricyclics (possibly because of its sedating effects), but there have been no systematic tests of this impression. As with MAO inhibitors, consistent predictors of tricyclic response are lacking as yet.

Fluoxetine

Recent reports of cases and open trials have suggested that the potent serotonergic reuptake inhibitor, fluoxetine, may be especially useful in treating PTSD. Fluoxetine used in 20 to 80 mg daily doses has been reported to alleviate not only hyperarousal and re-experiencing, but also avoidance, which is generally resistant to other pharmacotherapy. In one open trial (McDougle, Southwick, Charney, & St. James, 1991), 65% of patients responded to fluoxetine with a 50% or more drop in symptoms after four to

eight weeks of treatment. The drug has also been reported to produce relief of insomnia, nightmares, and flashbacks within 48 to 72 hours in chronic PTSD sufferers when used in conjunction with low doses of tricyclic antidepressants.

Benzodiazepines

There is little systematically collected data about use of benzodiazepines, and what exists is not very encouraging. Many of the reports about antidepressant use describe patients who had been on benzodiazepines for many years with little benefit prior to antidepressant therapy. Feldman (1987) conducted a chart review of 20 outpatient Veterans Administration hospital patients who had been taking alprazolam for from 1 to 12 months. Doses ranged form 0.5 to 6 mg daily. Sixteen of the 20 patients were reported to be improved, particularly in sleep parameters, mood, and anxiety and arousal levels. By contrast, Braun et al. (1987) found no significant difference between alprazolam and placebo in a double-blind, crossover study of 16 patients. Doses of alprazolam ranged up to 6 mg daily, and each leg of the trial lasted five weeks. There was some tendency for alprazolam to have mild anxiolytic effects in this study, but no effects on core PTSD symptoms.

In addition to questionable efficacy, there may be special problems with

the use of benzodiazepines in PTSD patients. In one study, attempts to withdraw patients from alprazolam produced severe rebound symptoms even though the dose was tapered very gradually. Prior heavy use of alcohol in this group may sensitize patients to benzodiazepine withdrawal in the same way that prior use of benzodiazepines themselves has been hypothesized to do.

Lithium

Lithium's mood stabilizing properties make it a plausible treatment for PTSD. No controlled studies have yet been done to test this hypothesis, but clinical evidence is somewhat positive. Kitchner and Greenstein (1985) presented a series of five PTSD patients who were treated with lithium. Doses ranging from 300 to 600 mg daily (producing blood levels in the 0.2 to 0.4 meq range) decreased rage, anxiety, nightmares, depression, and alcohol abuse. Patients were also found to make better use of psychotherapy on lithium than they had previously. These impressions were supported by van der Kolk (1987), who reported that 14 of 22 patients tried on lithium had decreased signs of autonomic hyperarousal, as well as decreased alcohol abuse. Systematic studies will be needed to confirm these preliminary results.

Carbamazepine

A kindling hypothesis of PTSD would suggest trials of carbamazepine and other mood stablizer/anticonvulsants for the disorder. Lipper et al. (1986) reported an open trial of 10 patients who received a mean dose of 666 mg daily for five weeks (mean blood level 8.2 g/ml). Seven of the 10 were substantially improved in symptoms related to intrusive memories, but not in avoidant behaviors, depression, or anxiety. Wolf, Alan, and Mosnaim (1988) describe a group of 10 patients openly treated with 800 to 1200 mg carbamazepine as being globally improved, but give no further details of the treatment or types of response.

Other Medications

A variety of other strategies have been reported sporadically in the literature. Blockers of alpha and beta adrenergic activity have been used with some success. Neuroleptics have generally not been advocated for PTSD because the risks of such drugs would be unacceptable for treating a nonpsychotic syndrome. However, some authors recommend their use acutely for sedating effects in patients who are agitated and difficult to control by other means.

OBSESSIVE-COMPULSIVE DISORDER

Clomipramine

Clomipramine is the best studied medication for treatment of OCD, with close to two dozen reports of controlled trials now in the literature. The salient early questions about clomipramine in OCD were whether it is really more effective than other tricylcic antidepressants, and whether its efficacy is due to a true antiobsessional, rather than antidepressant action. The weight of current evidence is positive in both regards.

Clomipramine has been found superior to placebo in about two-thirds of the double-blind studies done to date, and all of those that are methodologically adequate (Clomipramine Collaborative Study Group, 1991). The overall rate of clinically meaningful response to clomipramine (variously defined) is about 70%, compared to placebo responses which are generally under 20%. Out of eight studies in which clomipramine has been blindly evaluated against other tricyclics or MAO inhibitors, six have clearly favored clomipramine, one has been equivocal, and one has found no difference between either active drug and placebo.

The anti-obsessional effect of clomipramine is separate and independent from its antidepressant effect, and occurs in obsessive-compulsive patients with little or no concurrent depression (Katz & DeVeaugh-Geiss, 1990). While investigators have generally found that both depressive and obsessive-compulsive symptoms are alleviated by effective pharmacotherapy, the weight of current opinion is that the depression lifts

secondarily to the relief of burdensome obsessive-compulsive symptoms.

The mean maximum daily dose of clomipramine in controlled studies is about 250 mg, and the mean daily dose is 174 mg. Although formal dose response studies have not been done, those studies using markedly lower doses have tended to show poorer results. Stern, Marks, Mawson, and Luscombe (1980) have found that plasma levels in the range of 100 to 250 ng/ml of clomipramine are associated with better response than levels outside that range after 10 weeks of treatment. At the same time, levels of the metabolite desmethylclomipramine in the range 230 to 550 ng/ml were associated with better antidepressant, but not antiobsessional response.

Other authors have reported better anti-obsessional response in patients with clomipramine levels above 200 ng/ml. These reports suggest that low doses and blood levels may be important factors in medication nonresponsiveness.

There is general agreement that robust anti-obsessional response takes longer than antidepressant responses in patients suffering from primary depression. Length of controlled trials has ranged from 4 to 36 weeks, with a mean of about 11 weeks. Most studies have not found significant drug effects before 5 to 10 weeks, and several authors have noted that patients often continue to improve for the first several months of treatment. As with other

anxiety disorders, however, there may be considerable interindividual variability in response times, since some investigators have reported significant medication effects after as little as one to two weeks.

In general, obsessional thoughts and compulsive rituals respond about equally well to clomipramine treatment. Case reports have suggested that atypical variants such as hair pulling (trichotillomania), obsessional religious scrupulosity, bowel and other somatic obsessions, intrusive musical material, and depersonalization may respond to clomipramine as well as classic obsessive-compulsive symptoms (Swedo et al., 1989).

No consistent predictors of clomipramine response in OCD have yet been identified. Age, sex, duration of illness, baseline severity of obsessive-compulsive or depressive symptoms, predominance of obsessions versus compulsions, bizarreness of ideation, ability of the patient to resist ritualizing, and Axis II comorbidity have not been found to relate to outcome. However Jenike, Baer, Minichiello, Schwartz, and Carr (1986) have reported poorer outcomes in OCD patients with schizotypal personality disorder which, as part of the schizophrenia spectrum, may represent a special case.

While medication tends to produce global improvement, it is generally of moderate degree. Controlled studies average 42% symptom reduction with clomipramine (compared with 5% on placebo and about 15% on less

serotonergic antidepressants) which represents a substantial improvement in patients' ability to cope with their symptoms, but not a complete remission of the disorder. Thus, 50% or more of patients may be expected to continue to meet criteria for OCD after medication treatment.

Patients have been followed on clomipramine for over two years and have been found to maintain their therapeutic benefits. However, when medication is withdrawn, relapse is common, ranging above 80% by some estimates (Pato, Zoher-Kadouch, Zohar, & Murphy, 1988). At the same time, patients may often be well maintained on less than their maximum acute dose.

Other Serotonergic Agents

A variety of relatively newer selective serotonergic agents, including fluoxetine, sertraline, and fluvoxamine, are promising additions to clomipramine for treatment of OCD. At present, the most widely used of these is fluoxetine, which has been reported effective in case reports, several open trials, and one controlled study (Pigott et al., 1990). Higher doses of this drug have been used for OCD than for depression, with systematic trials generally using a maximum of 80 mg daily. Authors report a 50 to 65% decline in severity of obsessions, compulsions, and depressive symptoms over the first two months of treatment, with a more shallow slope of improvement

thereafter. As with clomipramine, fluoxetine response does not appear to depend upon the presence of clinically significant depression. In the one blind comparison of fluoxetine and clomipramine to date, the two drugs were found essentially equivalent in therapeutic efficacy. However, patients reported fewer side effects on fluoxetine than on clomipramine in this study.

Sertraline is another serotonergic reuptake blocker that has recently become commercially available in the United States. It has been tested in two double-blind studies with OCD patients, one of which showed it to be significantly more effective, and the other found it to be no different from placebo. While serotonergic agents appear to be the most useful medications for OCD presently available, it remains for future studies to determine the range and possible differences in therapeutic efficacies among these drugs.

Non-Serotonergic Agents

Most of the literature on drugs other than specific serotonergic agents for OCD consists of case reports and uncontrolled studies, which do not suggest robust therapeutic efficacy. Furthermore, many investigators note that patients in controlled studies of serotonergic agents have often had unsuccessful trials of other antidepressant or anxiolytic medications. However, the literature does provide indications that such medications may be useful in individual cases, or for specific indications. Cyclic antidepressants

and MAO inhibitors have been reported helpful in isolated cases of OCD, especially in patients who have other types of anxiety symptoms, such as panic attacks, in addition to obsessions and compulsions (Foa, Steketee, Kozak, & Dugger, 1987; Jenike, Surman, Cassem, Zusky, & Anderson, 1983). Anxiolytic medications may also be beneficial in such patients, although there are case reports of OCD patients who have no other types of anxiety symptoms responding well to alprazolam or clonazepam in the usual anxiolytic doses. Buspirone, a nonbenzodiazepine anxiolytic with proven efficacy for generalized anxiety, has been reported to alleviate OCD symptoms in some cases, although reports are conflicting.

Other medications may be helpful in special subgroups of patients with obsessive-compulsive symptoms. Carbamazepine has been reported helpful in patients with a history of overt seizures, and lithium may alleviate obsessive-compulsive symptoms in patients with bipolar disorder.

Strategies for Treatment-Resistant OCD

A variety of augmentation strategies have been suggested for increasing therapeutic response in treatment resistant OCD patients. None have been tested in controlled studies, but the most promising appears to be adding a second serotonergic agent to one of the first-line drugs.

Probably the best studied combination to date is buspirone added to

fluoxetine. In two open trials (Jenike, Baer, & Bottolph, 1991; Markovitz, Stagno, & Calabrese, 1990), buspirone in 30 to 60 mg doses was added in patients who had had a well-established, but partial response to fluoxetine, resulting in additional improvement after 4 to 8 weeks. However, controlled studies of buspirone in combination with clomipramine or fluoxetine have not demonstrated any benefit of dual therapy (Pigott et al., 1992).

Other case reports have described further improvement after trazodone was added to fluoxetine therapy, or fluoxetine was added to clomipramine therapy. Methodological shortcomings make these reports difficult to evaluate. Similar issues cloud reports of improvement after the addition of lithium to clomipramine or other tricyclic antidepressants. Among the other strategies reported helpful in resistant cases have been 1-tryptophan, triiodothyronine, and clonidine added to first-line medications, or intravenous clomipramine in patients who have not responded to oral dosing, but there is little systematically collected data on these methods as yet. Controlled studies of lithium or thyroid hormone added to serotonergic drugs have not demonstrated any benefit over monotherapy to date (McDougle, Price, Goodman, Charney, & Heninger, 1991; Pigott et al., 1991). Addition of fenfluramine, a serotonin releasing agent, has been reported in several cases in which patients responded to clomipramine, fluoxetine, or fluvoxamine, but could not tolerate the therapeutic dose. The addition of 20 to 40 mg of fenfluramine allowed the patients to maintain therapeutic benefits on lower

doses of antidepressant than with monotherapy.

A special case of treatment resistance may be OCD patients who also meet criteria for schizotypal personality disorder. In one study of patients who had not responded to fluvoxamine therapy the addition of pimozide 6.5 mg or thioridazine, 75 to 100 mg daily resulted in improvement in 88% of patients who had tic spectrum disorders or schizotypal personality, but only 22% of those who did not (McDougle et al., 1990).

SOCIAL PHOBIA

Monoamine Oxidase Inhibitors

A great deal of current interest centers around the use of monoamine oxidase inhibitors in treatment of social phobia. These medications had been reported successful in treating mixed groups of patients with social phobias and agoraphobia, but early reports did not distinguish drug responsivity between the two. Studies of atypical depression have also found MAO inhibitors to be effective in dealing with interpersonal hypersensitivity. Such results suggested that MAO inhibitors might be effective in social phobia (Liebowitz, Gorman, Fyer, & Klein, 1985).

This hypothesis has been recently tested in two open trials and two controlled studies. In open trials, 72% of a total of 43 patients, many of whom

had done poorly on beta-blockers or tricyclic antidepressants responded well to phenelzine or tranylcypromine. Six of the patients did best at doses of no more than 45 mg phenelzine daily.

Controlled studies of MAO inhibitors have partially confirmed earlier impressions. Liebowitz et al. (1988) conducted a double-blind, eight-week comparison of phenelzine (mean daily dose 72 mg), atenolol, and placebo. They found that phenelzine was superior to both comparison groups on a broad range of measures related to social piiobia after four or more weeks of treatment. While 64% of phenelzine-treated patients were considered responders, only 36% of atenolol and 31% of placebo-treated patients were so judged. While the authors state that "atenolol is effective for patients with discrete performance anxiety, but not generalized social anxiety . . . [and] phenelzine appears effective for generalized social anxiety but not for discrete performance anxiety," they do not present data to support this impression.

These results were only partially confirmed by Gelernter et al. (1991) who compared exposure instructions plus phenelzine, alprazolam, or placebo to formal cognitive therapy with no medication in a 12-week, double-blind trial. For phenelzine patients, 60% compared to 28% of alprazolam, 20% of placebo, and 24% of cognitive therapy patients were judged to be responders. However, only two items out of the seven assessment scales used showed

significant superiority of phenelzine, or indeed significant differences between conditions at all. At two months follow-up, phenelzine patients tended to maintain their gains better than patients in the other conditions. It is possible that the lower average dose of phenelzine in this study (55 mg daily) contributed to the somewhat equivocal therapeutic superiority.

Beta-Adrenergic Blockers

Reports of acute treatment of performance anxiety with beta-blockers suggested possible efficacy of these drugs in social phobia. An open trial of 10 patients with diagnosed social phobia (Gorman, Liebowitz, Fyer, Campeas, & Klein, 1985) supported this conclusion. They found that atenolol, given in 50 to 100 mg daily doses for six weeks resulted in some improvement in 90% of their patients, and marked improvement in 50%. In this study, efficacy was equivalent for patients with specific, versus generalized social phobias.

Two controlled studies have failed to find robust therapeutic effects of beta-blockers, however. Falloon, Lloyd, and Harpin (1981) conducted a study of 16 patients undergoing behavioral therapy plus either propranolol (160 to 320 mg daily) or placebo. While all patients improved, there was no added benefit of medication over the four-week trial. The more recent study by Liebowitz and colleagues using atenolol (50 to 100 mg daily) similarly failed to demonstrate superiority of the drug over placebo. While beta-blockers may

benefit patients with social or performance anxiety therefore, it is not clear whether they confer added benefit over education and exposure instructions.

Benzodiazepines

Three open trials provide evidence that benzodiazepines may be helpful to patients with social phobia. Reich and Yates (1988) using alprazolam (mean daily dose 2.9 mg), and Munjack, Baltazar. Bohn, Cabe, and Appleton (1990) and Reiter, Pollack, Rosenbaum, and Cohen (1990) using clonazepam (dose range 0.75 to 6 mg daily) reported clinically significant improvement in 60 to 80% of those treated. Patients improved on most measures within two weeks, but dimensions such as fear of negative evaluation and social avoidance, which may require practice and social relearning appeared to improve more slowly. Patients with both generalized and specific social anxiety have been reported to improve in these studies. The one controlled study of benzodiazepines to date, as mentioned above, found that patients improved on alprazolam, but not to a greater degree than those receiving cognitive therapy or simple exposure instructions with no medication. Thus, as with beta-blockers, the specific contribution, if any, of benzodiazepines to treatment of social phobia is not yet clear.

Other Medications

While patients undergoing treatment trials for social phobia often report previous lack of response to tricyclic antidepressants, no systematic studies of these drugs have yet been in such patients. Anecdotal reports suggest that tricyclics may be helpful in socially phobic patients with mitral valve prolapse, and this may be true of others as well.

Isolated reports of other treatments have recently appeared in the literature. In one case, a patient with social phobia who had not responded to alprazolam, propranolol, or phenelzine, improved rapidly when given clonidine 0.1 mg twice daily. Munjack et al. (1991) reported on an 8-week open trial of buspirone in 16 patient (maximum dose 60 mg daily). Over one-third of patients dropped out before completion of the study, but 80% of completers benefited to a moderate or marked degree. When corrected for the number of statistical tests performed, however, the degree of improvement was no longer significant. Further trials with these medications will be needed before any conclusions can be drawn.

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