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Are there Anticompulsive or Antiphobic Drugs? Review of the Evidence

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Summary: Review of 19 uncontrolled studies of antidepressants in phobic and in obsessive-compulsive disorders suggests that such drugs do not act reliably in the absence of symptoms of anxiety-depression (dysphoria). In dysphoric patients the drugs have a broad-spectrum effect, not only reducing phobias and rituals but also anxiety-depression, panic, anger, and hostility, all of which are highly intercorrelated, but none yet demonstrated to be the core disturbance. Phobics, but not obsessive-compulsives, have an unusually high dropout rate from treatment when drugs or placebo are given. When antidepressants are stopped, even after 6–8 months, relapse is likely. The drugs do not reduce the liability of many phobics and obsessive-compulsives to have dysphoric episodes over the years. Exposure treatments are more lastingly effective for phobias and for rituals, but do not reduce the liability to later dysphoric episodes.

Anxious-depressed mood (dysphoria) is common in phobic and obsessive compulsive syndromes. This paper summarizes evidence that when such dysphoria is absent antidepressant drugs have little effect on phobias and rituals. Dysphoric symptoms are similar to 'demoralization' and 'psychic distress', and do not amount to the syndromes of generalized anxiety state, dysthymia or depressive illness. Though they differ in important ways, both the symptoms and the syndromes of anxiety and depression also overlap considerably and are often indistinguishable (reviewed by Marks, 1983), while their relationships to one another and to phobias, rituals and spontaneous panic, are still problematic.

There are 19 controlled double-blind studies of antidepressants for predominantly phobic or obsessive-compulsive patients which included a minimum of eight patients who completed drug treatment. Space prevents detailed description of each study, but Table I summarises their main features. Drug doses were in the ranges usually considered adequate for depressive illnesses.

All but two of the studies concerned mainly female, adult populations aged 20–60 with chronic problems of 1–10 years duration or more; the exceptions are two studies of school-phobic children (Gittelman and Klein, 1971; Berney *et al*, 1981). Most concerned outpatients, though three involved inpatients who were obsessive-compulsive (Marks *et al*, 1980; Thoren *et al*, 1980; Insel *et al*, 1983), and 2 involved volunteers (McNair and Kahn, 1981; Telch, 1983). The obsessive-compulsives had pronounced rituals. Except for the school phobic studies, the phobics were largely agora- and social phobics with panic attacks and anxiety-depression (dysphoria). Anxiety-depression was a symptom, not a diagnosis, as most studies excluded patients who had either severe depression as a symptom or depressive illness as a diagnosis. Important differences between some of the agoraphobic samples are dealt with later. One study included a group of simple phobics (Zitrin *et al*, 1978).

Most reports had no or only very brief follow-up after drug treatment ceased. There are some exceptions reporting one or two-year follow-up (Zitrin *et al*, 1980; Tyrer *et al*, 1973 (described in Tyrer and Steinberg, 1975); Marks *et al*, 1980, 1982 (the latter also reported 2-year follow-up in Mawson *et al*, 1982)). Cross-study comparisons are difficult to make because of variation in descriptions of the samples and in methods of measurement and analysis of outcome, but Table I shows several trends. Unless otherwise noted, significant between-group drug effects imply that the antidepressant drug group improved significantly more on that variable than did the comparison group. Within-group effects imply that the drug group improved from start to end of treatment.

All four studies of obsessive-compulsives found a significant drug effect on obsessive-compulsive pheno-

TABLE I

Controlled studies of antidepressants in phobics and obsessive-compulsives

OBSESSIVE-COMPULSIVES	Drug	Duration given (weeks)	Sig. drug effect on: Dep.	Obs./Comp.	Panic	Drug effect present in initially: More Dep.	Less Dep.	Number of completers/drug cell	% Dropouts Drug	Placebo	Relapse after drug withdrawal Drug	Placebo
Marks *et al*, 1980	Clomipramine	36	+	+	anxiety	+	−	20	11		yes	[l] no
Thoren *et al*, 1980	[a] „	5	+	+	?	+	[b] −	8	4		yes	
Ananth *et al*, 1980	[c] „	4	(+)	(+)	?	?	?	10	?		?	
Insel *et al*, 1983	[d] „	6	+	+	?	+	+	12	14		yes	
ADULT PHOBICS					Phobia							
Telch, 1983	Imipramine	8	+	[n] −	[n] −	?	?	10	20	20	?	?
Zitrin *et al*, 1978	Imipramine	26	?	+	?	?	?	[e] 43	26	[d] 17	26%	[f] 11%
„ „ „ 1980	„	26	−	+	+	?	?	29	29	29	27%	[g] 6%
Marks *et al*, 1983	„	26	−	−	−	no drug effect		23	36	39	no drug effect	
Mavissakalian, 1983	„	12	+	+	−	?	?	24	25	20	?	
McNair & Kahn, 1981	[i] „	8	+	−	+	Drug×initial/ Dep. interaction		13 19	33	21 [m] 24	[h] yes	
Sheehan *et al*, 1980	[k] „	12	+	+	anxiety	veg. signs—no effect, mood not tested		19				
„ „ „	Phenelzine	12	+	+	„							
Solyom *et al*, 1981	„	8	−	−	?	no drug effect		?10		?	no drug effect	
Tyrer *et al*, 1973	„	8	−	+	−	?	?	14	27	11	yes	
Mountjoy & Roth, 1974	„	4	?	−	?	no drug effect		?13	?		no drug effect	
Lipsedge *et al*, 1973	Iproniazid	8	?	−	anxiety	?	?	32	23	7	yes	
Pecknold *et al*, 1980	[j] Clomipramine	10	(+)	(+)	?	?	?	?16	18		?	
SCHOOL PHOBICS												
Gittelman-Klein, 1971	Imipramine	6	+	+	anxiety	?	?	16	24	10	?	
Berney *et al*, 1981	Clomipramine	12	−	−	−	no drug effect		27		?	no drug effect	

[a] also had ineffective nortriptyline group; clomipramine not sig. superior to nortriptyline.
[b] see analysis by Marks, 1981, p. 176.
[c] comparison with ineffective amitriptyline, not placebo; clomipramine not sig. superior to amitriptyline.
[d] also had ineffective clorgyline group.
[e] excluding simple phobics, who did not respond to imipramine.
[f] follow-up at 1 year.
[g] „ „ 6 months.
[h] personal communication.
[i] comparison with chlordiazepoxide, not placebo.
[j] „ „ and without tryptophan, not placebo.
[k] imipramine did not differ sig. from phenelzine (Sheehan *et al*, 1980).
[l] all patients had exposure in vivo.
[m] chlordiazepoxide, not placebo.
[n] had anti-exposure instructions.

+ = effect present.
− = „ absent.
? = not reported.
() = improvement significant within-groups, not reported between groups.
Dep. = depression.
Obs./Comp. = Obsessive-compulsive.

mena and depression, though one of these was only significant within, not between, groups (Ananth *et al,* 1980). Of the thirteen studies of adult phobics, seven found significant drug effects on phobias, one of these only being significant within, not between, groups (Pecknold *et al,* 1982). One study of school phobics, using imipramine reported a significant drug effect on phobias (Gittelman and Klein, 1971), while the other, using clomipramine, did not (Berney *et al,* 1981); the former used 100–200 mgs a day, the latter 40–75 mgs a day.

Of the 10 studies of adult phobics which reported outcome of depression, 6 found a significant drug effect, 2 of these being only within-groups (Pecknold, 1982; Telch, 1983); 4 studies found no drug effect, while 3 did not report outcome of depression. One school phobic study found a drug effect on depression (Gittelman and Klein, 1971) while the other did not (Berney *et al,* 1981).

As a rule, where target (phobic or obsessive-compulsive) problems improved so did depression, and where target problems did not improve neither did depression. Of the 15 studies which analyzed outcome of both, 11 found concordance of improvement or no-change across target problems and depression, the exceptions being Zitrin *et al* (1980), and Tyrer *et al* (1973) both of whom found improvement in phobias but not in depression, and both McNair and Kahn (1981) and Telch (1983) who noted that depression improved but phobias did not.

One only of the four studies of obsessive-compulsives reported outcome on anxiety, there being a drug effect concordant with that on rituals and on depression (Marks *et al,* 1980). Of the thirteen studies of adult phobias, outcome of panics was reported in only 6, drug effect being present in 2 studies (Zitrin *et al,* 1980) and McNair and Kahn (1981) and absent in 4 (Marks *et al,* 1983; Mavissakalian, 1983; Tyrer *et al,* 1973; Telch, 1983). Three more studies reported a drug effect on anxiety and did not report on panics.

Only 9 of the 19 studies reported outcome in both anxiety or panic on the one hand, and depression on the other. Of these 9, 6 were concordant for improvement or no-change across depression and anxiety or panic. The exceptions were Zitrin *et al* (1980), who noted improvement in panics but not in depression, Mavissakalian *et al* (1983) and Telch (1983) who both found reduction of depression but not of panic. It is relevant here that in anxiety disorders, too, imipramine was more effective than chlordiazepoxide or placebo in reducing depression as well as anxiety (Kahn *et al,* 1981).

When present in phobic and obsessional syndromes, the drug-effects of antidepressants are not restricted to phobias, rituals and anxiety-depression, but seems more widespread. In the few studies which report measures across a broad spectrum of different symptoms, antidepressant drugs usually improve them. As an example, Sheehan *et al* (1980, their Table I) found that imipramine and phenelzine patients improved significantly more than placebo patients on *every* measure, regardless of whether it concerned phobias, anxiety, 2 measures of depression, psychotension, hostility, interpersonal sensitivity, somatic, obsessive-compulsive and work-social scores. The same broad-spectrum improvement for rituals, depression, anxiety and social adjustment was found by Marks *et al* (Fig 2). Similarly, McNair and Kahn (1981) found an imipramine effect across a variety of problems such as panic, depression and anger, though not for phobias (Table II); the anger 'effect' could conceivably have resulted from disinhibition by benzodiazepines

TABLE II

Broad spectrum effect of imipramine in agoraphobics: efficacy summary for completers at week 8 (from McNair and Kahn, 1981)

Criterion	Imipramine effect	Imipramine×depression	Imipramine×phobic severity
Agoraphobia	–	.05	.05
Phobic anxiety (SCL)	–	.05	.05
Panic	.05	–	–
Tension-anxiety (POMS)	.1	–	.05
Depression (SCL-self)	.05	–	–
„ (SCL-dr.)	.05	–	.01
„ (POMS)	.1	–	–
„ (Beck)	–	?	.05
Anger (SCL-self)	.001	.05	.001
„ (SCL-dr.)	.05	–	–
„ (POMS)	.001	–	.01
Somatic (SCL-self)	.1	.1	.05
Global improvement	–	–	.05

.05, .01 etc. = Sig. on Ancova; – = NS.

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rather than from improvement by imipramine. We do not yet know whether initial dysphoria is a better predictor of drug effect than is initial panic, anger or hostility. Level of initial rituals or phobias has not been a good predictor where it has been examined. Nor do we know whether there is a central effect with generalization to other areas, or whether we are observing numerous independent effects.

In the interesting study of Telch (1983) no broad-spectrum drug effect was found, imipramine improving depression only. These subjects also had anti-exposure instructions 'to rest and refrain from entering phobic situations. Contrast groups in this study had exposure in vivo with either imipramine or placebo. The imipramine-exposure group improved concordantly for depression, panic and phobias, while placebo-exposure patients improved in phobias and in panic but only slightly in depression.

Initial dysphoria and outcome of treatment

One predictor of drug effect seems to be the starting level of dysphoria, drug effects generally being absent where this is low. Lack of common measures across studies complicates the task, but paired comparisons of studies were possible on four common measures (Table I). The first measure was initial mean Hamilton depression score; this was 6 and 8 where drug effects were absent (Marks *et al*, 1980, 1983) but 15, 15 and 27 where drug effects were present (Insel *et al*, 1983). The 2nd comparison was on the initial mean Zung depression score, which was 45 where drug effect was absent (Solyom *et al*, 1981 and personal communication) but 54 and 63 where drug effect was present (Sheehan *et al*, 1980; Mavissakalian *et al*, 1983). The 3rd comparison was on initial mean CPRS depression score, which was 12 where drug effect was absent but 25 where this was present (Thoren *et al*, 1980).

The London sample of Marks *et al* (1983) was not only significantly less dysphoric, but also slightly *more* agoraphobic than the Boston sample of Sheehan *et al* (1980). Seventy-three per cent of London patients but only 56 per cent of Boston patients rated extreme fear of going out alone far from home ($P < .1$ on χ^2). London and Boston patients thus did not differentially respond high or low to questions as a whole (no difference in response set), but rather to certain types of symptom (they differed in the kinds of symptoms

TABLE III

Outcome versus initial depression score
Controlled studies of phobics and obsessive-compulsives

	Initial mean depression score	
MODERATE	MODERATE–MILD	MILD–ABSENT
Drug effect present		
Ananth *et al*, 1980 (psychiatric rating 60)	Gittelman-Klein and Klein, 1971 (⅓ rated depressed)	? Zitrin *et al*, 1980 (6% extremely dep.)
Marks *et al*, 1980 (+Hamilton 15, *27)	Insel *et al*, 1983 (Hamilton 15—[21 item])	
McNair and Kahn, 1981 (SCL90—2.2)	Mavissakalian *et al*, 1983 (Beck 13, Zung 54)	
Pecknold *et al*, 1982 (+Hamilton 26)	Tyrer *et al*, 1973 (Gelder-Marks 2.8 on 0–8 scale)	
Sheehan *et al*, 1980 (SCL90—2.2) (Zung 63)	? Zitrin *et al*, 1980 (BPRS 1.5 on 0–4 scale)	
Thoren *et al*, 1980 (CPRS 16, *25)		
Drug effect absent		
**Telch, 1983	Berney *et al*, 1981	Marks *et al*, 1980 (Hamilton *6)
(Zung 67, Beck 25)	(44% rated depressed)	„ „ „ 1982 („ 8)
		Solyom *et al*, 1981 (Zung 45)
		Thoren *et al*, 1980 (CPRS *12)

\+ 17-item.
* subsamples. **imipramine patients had anti-exposure instructions

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they emphasized). These comparisons highlight the difficulty in obtaining closely comparable populations across centres merely by utilizing diagnostic categories alone, and illustrate the additional need to report initial phenomenological features on standard measures and for cross-centre calibration like that carried out in the US/UK study of depression and schizophrenia.

A coarser way of judging the effect of dysphoria is by grouping the studies according to initial levels of dysphoria, regardless of the particular measure used (Table III). The lower right sector of Table III shows that in 4 of the 6 samples or subsamples where a drug effect was absent the starting level of dysphoria was especially low. The exceptions are Telch (1983), where patients *did* have initial dysphoria and imipramine reduced depression but not phobias or panics, and Berney *et al* (1981) in whose school phobias clomipramine had no significant effect. The placing of the sample of Zitrin *et al* (1980) is unclear, because on the BPRS rating scale it would be rated as mild-moderately dysphoric, yet on another item (Klein, written communication) it would be mild-absent.

Within three of the studies on obsessive-compulsives, direct comparison was possible between patients with higher and lower levels of initial dysphoria. Two of these comparisons showed that the effect of clomipramine was exclusively attributable to those patients with the highest levels of dysphoria at the start, and was absent in those with initially low levels. For example, when improvement in depression is studied from the data of Thoren *et al* (1980) (Fig 1) all 3 of the 8 clomipramine patients who had secondary depression responded in the open part of the study, while only one of the 5 without secondary depression responded (these were also the 5 patients with the highest plasma levels of clomipramine (Åsberg, oral communication). During the initial 5-week controlled phase of the study, patients with initial depression subsequently improved significantly more than those without it (Fig 1). Fig 1 also shows that the higher initial values of obsessive-compulsive phenomena in those who were initially depressed is unlikely to account for their greater improvement with

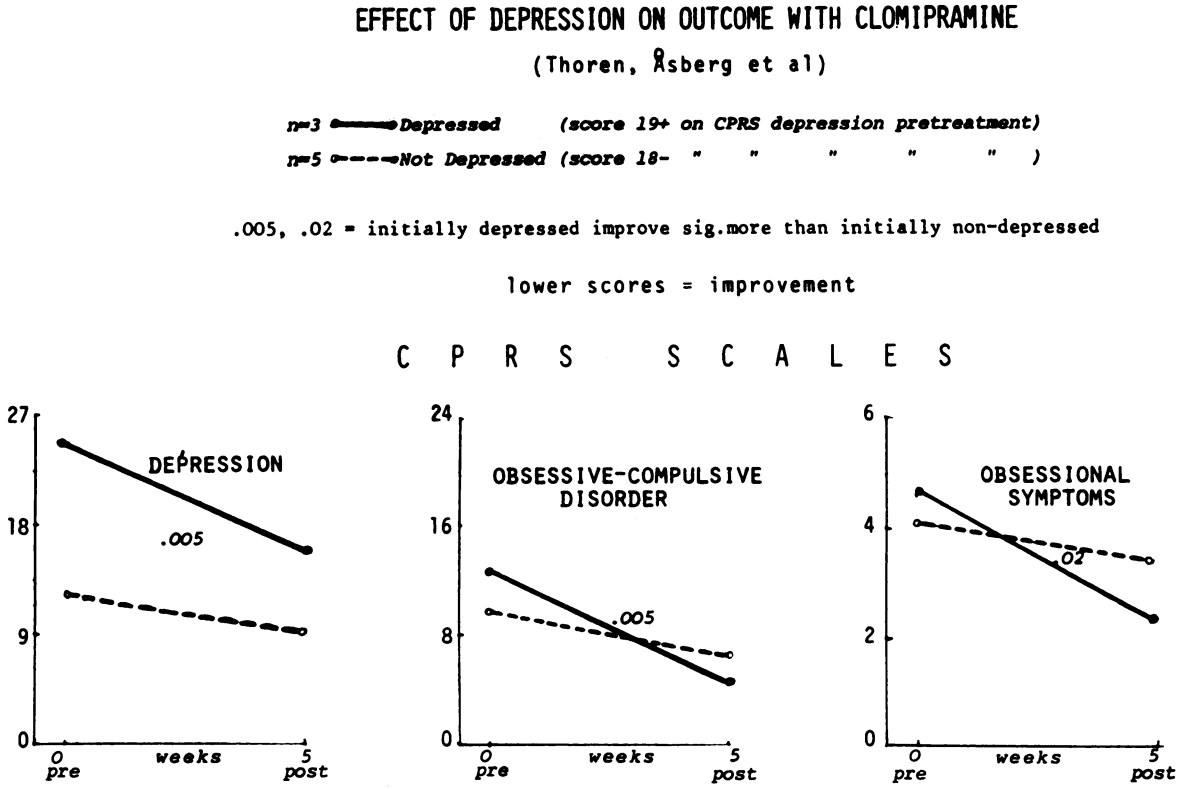

FIG 1.—Outcome of ritualizers with clomipramine: Initially high versus initially low depression (data from Thoren *et al*, 1980). CPRS depression improvement scores were kindly supplied by Dr Marie Åsberg.

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clomipramine, as these phenomena improved to a level substantially less than that reached by those patients who were initially not depressed.

A similar analysis is shown for the ritualizers of Marks *et al* (1980) (Fig 2); here the two samples represented the highest and lowest quartiles for depression on the Hamilton and Wakefield scales and the two middle quartiles were omitted. Between weeks 4–10 *all* patients had exposure in vivo treatment as well as medication, which explains the steep slope of improvement during that period. Drug effects show up as divergence between the two slopes. As in the study by Thoren *et al*, the clomipramine effect (shown here by significant divergence of slopes) occurred exclusively in those with the highest starting levels of depression. Further analysis of these patients (Mawson *et al*, 1982) found that a single 0–8 scale for initial free floating *anxiety* was almost as good a predictor of clomipramine effect as was depression. This is not surprising in view of their intercorrelation of .7, but suggests that we should speak of dysphoria rather than depression.

Could the drug effect and dysphoria be associated merely by a statistical artefact arising from patients with no dysphoria tending also to score lower on all other measures and thus having no room to improve on their scales. A glance at Figs 1 and 2 will show that this does not account for the association. In Fig 1, with ritualizers who had no exposure, the initially non-depressed subsample ended up worse than the initially depressed subsample, even though they had begun better. In Fig 2, the initially non-depressed ritualizers began better than the initially depressed ritualizers (left side of Figure), and also ended up better, showing no floor effect either for target rituals or for leisure adjustment, though there was one for depression. Improvement occurred during exposure in vivo given during weeks 4 to 10. That clomipramine had an obvious effect in the initially depressed and no effect in the initially non-depressed cannot be attributed to statistical artefact.

A third comparison had discordant findings. Insel *et al* (1983, personal communication) compared outcomes of his obsessive-compulsives who had the highest and lowest initial depression scores, and found that both subsamples retained the superiority of clomipramine over clorgyline. This analysis, however, included patients in the middle range, and it is not known how patients fared who initially had very low depression scores comparable to those in the

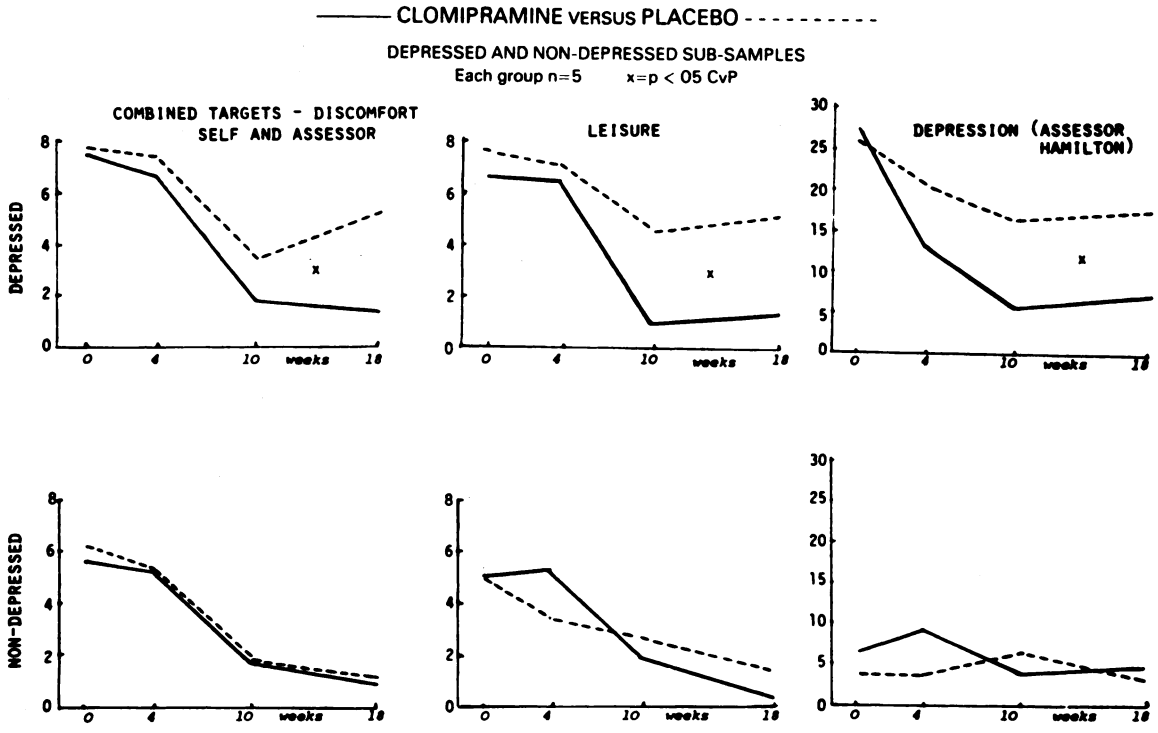

FIG 2.—Outcome of ritualizers with clomipramine: Initially high versus initially low depression (from Marks *et al*, 1980).

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subsamples of Thoren *et al* (1980) and Marks *et al* (1980).

Among phobics, McNair and Kahn (1981) found that imipramine had no significant drug effect on agoraphobia overall; a significant agoraphobia×depression interaction indicated that imipramine reduced agoraphobia only when it was accompanied by depression (Table II). Imipramine did produce a significant reduction in depression and also in panics independently of depression.

Zitrin *et al* (1980) found a negative correlation between starting level of depression and several measures of outcome, but did not compare outcomes of those with the highest and lowest starting levels, which might have detected effects obscured by their many patients in the middle starting level. The potential importance of this point is testified by the obvious relationship between initial depression and outcome in the ritualizers of Marks *et al* (1980) when the top and bottom quartiles were compared, but the virtual disappearance of this relationship when it was sought for in the entire sample (Raskin, oral communication). Sheehan *et al* (1980) found no relationship between 5 vegetative signs of endogenous depressive illness and outcome. Working with their data this author too could find no relationship between outcomes contrasted in patients with the highest and the lowest levels of initial depression. However, even those with the lowest levels had fairly high starting levels (only 2 had Zung scores below 55). Table III suggests that there may be a threshold of moderate dysphoria below which a drug effect is unlikely, and the Boston sample had too few cases without dysphoria to test this idea.

Of the 13 patients in adult phobics, 6 found no drug effect on phobias. Of these 6, in 2 patients had low initial levels of dysphoria (Marks *et al*, 1980; Solyom *et al*, 1981), in one depression and panic improved but phobias did not (McNair and Kahn, 1981), in another depression improved but phobias and panic did not (Telch, 1983), and 2 did not report initial depression levels (Mountjoy *et al*, 1977; Lipsedge *et al*, 1973). The predominantly agoraphobic sample of Mountjoy *et al* (1977) did not improve significantly on agoraphobia or on depression, only on a social phobia scale; all these patients had, in addition to phenelzine, a daily dose of 15 mgs diazepam and 10 mgs nitrazepam, which confounds interpretation. In the agoraphobics of Lipsedge *et al* (1973) iproniazid had a significant effect on phobic anxiety but not on phobic avoidance.

In keeping with the studies shown in Table I is a report concerning patients who had a diagnosis of primary depression of at least 4 weeks' duration, often with additional phobic symptoms (Nies and Robinson, 1981). These phobias accompanying depression responded to either phenelzine 60 mgs daily (but not 30 mgs) or to amitriptyline 150 mgs daily.

Few comparisons are available between different antidepressants. For ritualizers clomipramine was effective in all 4 studies which used it, but was not significantly superior to nortriptyline or amitriptyline while nortriptyline, amitriptyline, and clorgyline were each ineffective in one study (Thoren *et al*, 1980; Ananth *et al*, 1980; Insel *et al*, 1983). Antiphobic effects were found for imipramine in 5 of 7 studies, for phenelzine in 2 of 4 studies and for iproniazid and clomipramine in one study each. For phobics, between-drug comparisons are only available in one study, for phenelzine versus imipramine (Sheehan *et al*, 1980); there was little to choose between them.

Problems of drug treatment

In most of the phobic and obsessive-compulsive populations reviewed in this paper the disorder had been present for 1–10 years or more by the time treatment began. In such chronic populations treatments are more valuable if their benefits last for years after the treatment ceases. Unfortunately, this is not true for antidepressants. Where a drug effect was found, there was a high relapse rate on stopping the drug, even after it had been taken for 6–8 months. This is a drawback to drugs whose side effects over long periods are unclear. It indicates that the pathology is being suppressed rather than cured by such drugs, and there is a tendency for the mood disturbance to persist fluctuatingly over years. The pattern of relapse following drug withdrawal even after prolonged drug administration is similar to that found with antidepressants in depressive illness, phenothiazines in schizophrenia and cimetidine in duodenal ulcer.

Another drawback to antidepressants is the high dropout rate found by almost all authors in phobics, these mostly being from a quarter to a third (Table I). Interestingly, dropouts are common with placebo as well, suggesting that phobics are poor pill takers. Often they misinterpret pre-existing somatic complaints as drug side effects as soon as they start the drug. In contrast, the only three studies to report dropout rates with obsessive-compulsives did not find these to be high (Table I), comparing well with the 16 per cent dropout rate for behavioural treatments as a whole in several hundred neurotic patients treated in the author's unit.

Discussion

Many studies of antidepressants in obsessive-compulsive and phobic disorders have found a significant broad-spectrum drug effect, reducing not only

rituals and phobias but also depression, anxiety, panics, anger and other psychopathology. It might be misleading to concentrate on spontaneous panics as the focus of drug action in agoraphobia, as some authors do (Sheehan *et al,* 1980; Zitrin *et al,* 1978, 1980). Imipramine and phenelzine can undoubtedly block panic attacks, but they also block a lot of other cohering pathological features, if not simultaneously, then at the same times that they are measured. It is illogical to accept any one of those features as primary unless and until detailed analysis has shown that change in that feature precedes change in the other aspects. As yet there is no firm experimental evidence for any core focus of action of antidepressants in these syndromes, and the belief in the importance of spontaneous panics as opposed to dysphoria is based only on clinical anecdote. Tyrer *et al* (1973) found no improvement in panics (rated for the previous 3 days) despite improvement in phobias. Zitrin *et al* (1980) are the only ones to actually report measures of panic which improved along with phobias, and even they did not demonstrate that panic improves before phobias, a sequence which needs to be demonstrated if antipanic drug effects are primary. In agoraphobics who received placebo plus behavioural treatment directed at their phobic avoidance panics improved significantly along with the phobias, and to the same degree as in patients who received imipramine plus behavioural treatment (Marks *et al,* 1983).

There is no experimental data substantiating the primacy of panics in agoraphobia. Panics are but one of several manifestations of disturbed *mood,* others being free floating background anxiety, and depression, all of which tend to occur together. The findings support the caution expressed by McNair and Kahn (1981) (pp 77–8) who conclude: "The mechanism of anticipatory anxiety reduction may be more complex than previously realized. In our small sample, there was a relatively broad range of depressive symptomatology, and rather strong evidence that imipramine more effectively alleviated depression. In addition, the most depressed (but also most phobic) cases reported the greatest reduction of agoraphobic symptoms with imipramine. These findings are not entirely congruent with Klein's views that relief of the agoraphobic component is also independent of depression or that imipramine is ineffective for anticipatory anxiety. All of this underlines the need for greater knowledge of the role of depression, both secondary and primary, in the development and treatment of the panic-phobic syndrome".

There was no drug effect in four samples of patients who had normal mood. Antidepressant drugs may require some minimum mood disturbance to be present before they can act in phobic and obsessive-compulsive disorders. Studies commonly report that drugs improve mood as well as phobias and rituals. Though several authors have found no significant correlation between initial depression and subsequent improvement in phobias or rituals, correlations of outcome with initial mood in samples which included many patients with slight-moderate dysphoria may obscure the absence of drug effects in patients with normal mood, i.e. who were below some minimum threshold of dysphoria. Most authors have not tested for this possibility, and in addition, some samples may contain practically no patients with normal mood in whom this idea can be examined.

Samples of patients from different centres can vary considerably in the proportions of patients they contain with disturbed and with normal mood (e.g. one London vs. one Boston sample of agoraphobics). This alone might account for most differences across centres in antidepressant drug effects in these syndromes. Future research studies could be better compared if they were to adopt a minimum number of standard measures. These might include the short Beck Depression Inventory and the Hamilton Depression Scale, target ritual or target phobia measures like those of Marks *et al* (1980 and 1983) and, for phobics only, the Fear Questionnaire of Marks and Mathews (1979) and panic scale of Zitrin *et al* (1980).

Plasma monitoring of drug levels is desirable, and a followup for a minimum of a year after cessation of the drugs is essential to check on relapse. Also necessary is report of absolute mean scores, standard deviations and cell size of each measure at each rating point from pretreatment to end of followup. Such data can be reported in one table taking up merely one journal page, and would greatly facilitate the task of comparing populations and effects across research centres.

The question arises why dysphoria is so common in phobic-compulsive syndromes as well as in generalized anxiety disorders, and how the mood disturbance differs in treated and untreated samples in the community and in the clinic. Further issues concern the frequency and natural history over the years of anxiety, depression, panic, phobias and rituals in different samples, why they intercorrelate so highly, why panics are so common in generalized anxiety disorder and agoraphobia and, to a lesser extent in social phobia, but are rare in obsessive-compulsive disorder, and what distinguishes panic or anxiety disorder without agoraphobia from panic or anxiety disorder with agoraphobia.

The DMS-III subdivisions of dysthymic disorder, panic disorder, generalized anxiety disorder and agoraphobia with and without panic attacks are not yet firmly based on hard scientific data showing that they have therapeutic or prognostic import. Symptoms of

anxiety-depression (dysphoria) are a frequent feature not only in all these and in obsessive-compulsive disorder but also in many physical disorders, and are also the commonest complaint in primary care populations across the globe. In one community survey "psychic distress", i.e. dysphoria, was present in 67 per cent of agoraphobics (Balter, oral communication). The level of dysphoria may vary considerably among samples and partly account for differences in drug effects. It is possible that dysphoria from varied causes may be as responsive to antidepressants as is inflammation of diverse origins to asprin, in both instances as long as the drug is given. We need to distinguish between drug effects on less specific features associated with a syndrome like inflammation or dysphoria from effects on more specific features like bacteria in the tissues, or ritualistic or phobic behaviour.

Contrast of antidepressant and exposure treatments

In contrast to the broad-spectrum action of antidepressants which tends to cease when the drug is stopped, the therapeutic action of exposure in vivo is both more specific and more lasting in phobic-compulsive syndromes. Exposure therapy improves phobias and rituals more than mood, and is only indicated where there is persistent avoidance of some discomforting situation or feeling. While marked dysphoria is associated with better response to antidepressant drugs it seems to retard improvement with exposure treatments. In the absence of marked dysphoria, gains in phobias and rituals continue over 2–9 years follow-up after completion of exposure treatment (Marks, 1981; Emmelkamp, 1982). Neither antidepressants nor exposure seem to reduce the tendency for many of these patients to continue having affective episodes over the years, though exposure treatment seems to uncouple their dual pathology by protecting against the full reemergence of rituals and phobias when mood disturbance subsequently recurs (Marks, 1981). Not only is exposure effective for even complex phobias and rituals, but it also need not be more time-consuming than drug-administration. Exposure is often successfully self-administered with the aid of a self-help manual (Marks, 1978) and brief guidance from a therapist (Ghosh *et al*, 1983). These points are important for psychiatrists to consider before embarking on antidepressant drug treatments which mainly act in the presence of dysphoria, are not without potentially serious side effects, and which are associated with a high relapse rate on drug withdrawal.

That imipramine alone is not enough, even in dysphoric patients, but rather acts by making it easier for patients to undertake everday exposure tasks, which they then habituate to, is suggested by the findings of Telch (1983). His imipramine patients had initial dysphoria and then improved in depression but not in phobias or panics; they were deliberately discouraged from carrying out exposure. Yet other patients who had imipramine plus exposure in vivo improved not only in depression but also in phobias and panics, as did other patients who had placebo plus exposure in vivo, though the latter group improved less in depression. The practical point to emerge is that dysphoric phobics and obsessive-compulsives who are given antidepressants should probably be encouraged to systematically reenter their phobia- or ritual-evoking situations as soon as possible.

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