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Review Article

Drug Treatment of the Personality Disorders

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Many people with well defined borderline and schizotypal personality disorders may benefit considerably from small doses of neuroleptics. Depression that occurs with personality disorders, which is frequent, responds poorly to tricyclics but may respond better to neuroleptics, while the response to ECT is usually short lived. Selected borderline subjects may respond to MAOIs, particularly where there is a history of childhood hyperactivity. Carbamazepine and lithium may help some individuals with episodic behavioural dyscontrol and aggression, even in the absence of epileptic, affective or organic features. Drug treatments can be combined with psychotherapy, but further placebo-controlled trials are needed to clarify which drugs are most useful, and whether there are any useful clinical predictors of drug responsiveness.

> "If anything is impressive in the literature on the treatment of the borderline syndrome it is that nothing seems to work very well or for very long." (Dryud, 1972)

The treatment of the personality disorders is a topic surrounded with much pessimism, and most clinicians firmly believe that these disorders are essentially untreatable and that subjects with a personality disorder have little capacity for change. Despite this, ever since the first description of the borderline syndrome by Stern (1938), a few psychotherapists have taken a keen interest in these patients, and over the last two decades there has been an increasing number of articles describing the techniques and difficulties of psychotherapy with the borderline. This implies that there are at least *some* psychotherapists who believe that *some* change may be possible for at least *some* patients, albeit with difficulty. Stone (1985) considers these patients to be "just barely treatable".

There has also been a steady trickle of drug studies, focusing mainly on the use of neuroleptics. The whole area of drug treatment has recently sprung to life with the publication of three large, well designed drug trials with properly defined groups of borderline and schizotypal subjects (Goldberg *et al*, 1986; Soloff *et al*, 1986*a*; Cowdrey & Gardner, 1988), and the topic was even given an editorial in the *Lancet* (1986).

The principal stimulus for these trials and the most striking advance in personality disorder research in recent years has been in the area of classification and diagnosis. Clear operational criteria are now available in DSM-III-R (American Psychiatric Association, 1987) for each category of personality disorder, and this has enabled drug trials to be conducted in well defined patient groups, although only borderline personality disorder (BPD) and schizotypal personality disorder (SPD) (Table 1) have been the focus of any systematic psychopharmacological research. Even though the term 'borderline personality disorder' is more commonly used in the American literature than the English, the condition is equally frequent in the UK. Kroll *et al* (1982), using Gunderson's diagnostic interview for borderlines

Table 1

DSM-III-R criteria for borderline and schizotypal personality disorders (the two categories where drug treatments have been applied)

Borderline personality disorder (BPD)	Schizotypal personality disorder (SPD)
(1) Unstable or intense interpersonal relationships	(1) Ideas of reference
(2) Impulsiveness which may be self-damaging	(2) Excessive social anxiety
(3) Affective instability	(3) Odd beliefs and magical thinking
(4) Inappropriate or intense anger, temper	(4) Unusual perceptual experience, e.g. illusions
(5) Recurrent suicidal threats or self-mutilation	(5) Odd or eccentric behaviour or appearance
(6) Identity disturbance	(6) No close friends (or only one) apart from first-degree relatives
(7) Chronic feelings of emptiness or boredom	(7) Odd speech which may be impoverished, vague or abstract
(8) Frantic efforts to avoid real or imagined abandonment	(8) Inappropriate or constricted affect
	(9) Suspiciousness or paranoid ideation

For both disorders the onset should be in early adulthood and at least *five* items are required to make the diagnosis.

(Gunderson *et al*, 1981), showed that 14.5% of the patients on an admission ward in Fulbourne Hospital in Cambridge had BPD, although only 8.5% fulfilled DSM–III criteria for BPD. English clinicians preferred to use the labels of 'hysterical', 'explosive' or 'immature' personality disorders for the same subject.

Personality disorders are common. Of all psychiatric admissions in the UK, 7.5% had a personality disorder (Department of Health and Social Security, 1985), and a figure of 7.5% for BPD has been given for the USA (Soloff, 1981). The personality disorders also have a considerable morbidity and mortality. Thus the standardised mortality ratio for the 20–39-year age group is raised sixfold, a rise similar to that reported for schizophrenia and affective disorder (Zilber *et al*, 1989).

From a purely pragmatic point of view, psychotropic drugs are often prescribed to BPD in-patients, yet this is done without any empirical guidance or definite indications. Androlunis *et al* (1982) concluded from a survey of fellow clinicians that 84% of women and 87% of men with BPD received medication while in hospital, yet the clinicians in the survey admitted they had no clear reasons for selecting the particular drugs they prescribed. Soloff (1981), in a retrospective study, reported that 53% of an in-patient sample with BPD received medication and of these, 62% showed "clear and unequivocable progress" compared with only 18.7% of those who received no medication.

Although it is clear that large numbers of individuals with personality disorders are being medicated during their stay in hospital, there are no guidelines in the literature on drug use, nor is the topic considered in any of the major textbooks on psychiatry (Hill *et al*, 1986; Kendell & Zealley, 1988; Gelder *et al*, 1989; Kaplan & Sadock, 1989). As Chessick (1969) aptly put it, "these individuals seem to lie on the periphery of psychiatry, on the periphery of society and the periphery of penology".

This review focuses on the recent major drug trials. These studies are of three types: firstly there are a few studies where the effect of a drug on a specific personality disorder is examined; secondly, there are those studies which focus on a specific syndrome or behaviour pattern in subjects with a personality disorder; and thirdly there are a few studies of the effect of drugs on DSM–III–R axis I disorders such as depression in BPD subjects. In addition, some of the older literature appertaining to drug effects among subjects with personality disorders is considered. To merit inclusion in this review, a study should describe the effects of a pharmacological agent on a patient, or a group of patients, with a primary diagnosis of personality disorder. Some drug studies in other disorders where the prevalence of the personality disorders is known to be high have also been included. These are disruptive delinquents, aggressive prisoners, clinic alcoholics, recurrent parasuicides, aggressive and self-mutilating mentally handicapped subjects, and adults with attentional deficit disorders. The emphasis throughout this review is on the effects of drugs, beneficial or otherwise, on the personality disorder, rather than their known effects or side-effects on normal volunteers, or on patients with DSM–III–R axis I disorders.

Low-dose neuroleptic therapy – early uncontrolled studies

The introduction of chlorpromazine for the treatment of schizophrenia by Delay *et al* (1954) dramatically advanced the science of therapeutics in psychiatry. The discovery of the very much lesser but also beneficial effect that small doses of neuroleptics sometimes have on subjects with personality disorders has been a much slower, more haphazard, and less publicised affair. The earliest observations were made by a few American psychoanalysts who had a long-standing interest in borderline personality disorder.

Winkleman (1955) was the first to report the relief chlorpromazine gave to neurotic symptoms, particularly agitation, anxiety, phobias, and obsessions, as well as confirming its effects in acute schizophrenia. Winkleman (1975) described his experience with neuroleptics as adjuvant treatment to 30 of his own patients who were attending for psychoanalysis:

> "during drug months using a phenothiazine, a diminished intensity of what are classically called id drives and derivatives was observed, which allows psychotherapy to proceed more effectively. Anxiety was reduced and primary process material seemed less threatening and was also more amenable to interpretation. There was improved reality testing, better interpersonal relationships and less fantasy, symbolisation and displacement. In proper dosage and at the proper time these neuroleptic effects benefited the psychotherapeutic process".

Other analysts such as Schmideberg (1959) and Kernberg (1968) also suggest the use of tranquillising medication when a borderline patient's anxiety begins to interfere with analysis. Mandell (1976) also mentions the use of a small dose of a neuroleptic in a borderline subject to help "tighten up his associations". Needless to say, not all analysts with an interest in BPD were so favourably disposed to neuroleptics. Dryud (1972) wrote, "phenothiazines, which should theoretically help with the postulated lack of central inhibition, have in my experience yielded no improved affect; possibly they lengthen

the periods of unpleasant affects and in a larger dose result in depressed behaviour".

A second and quite independent impetus to the exploration of the role of neuroleptics in the personality disorders came from Belgium, where the pharmaceutical company Janssen had recently synthesised pimozide, a potent dopamine receptor antagonist, and they sought to explore its role in all categories of psychiatric illness. Reyntjens *et al* (1972) supported by Janssen gave 2–8 mg pimozide (mean dose 3 mg) to 120 patients with DSM–II personality disorders (American Psychiatric Association, 1968) and found an excellent global outcome in 69% of subjects. His study was subsequently replicated by Collard (1976) using a lower dose of pimozide (1–2 mg daily). He studied his patients for up to nine months, and showed that beneficial effects often took up to three months to appear, but between three and nine months there was little further improvement.

The next significant contribution was made in the UK by Perinpanayagam & Haig (1977) working with a much more severely disturbed in-patient group. They described ten seriously disturbed adolescent girls who were in a secure unit, and wrote:

> "they were disturbed, violent and aggressive girls, two of whom had schizophrenia, who were not influenced by tender loving care and they were started on depot tranquillisers. The girls on this regime benefited, in that their disturbed behaviour subsided. They became approachable in the psychotherapeutic framework and were more co-operative and psychologically more stable".

In the USA, Brinkley *et al* (1979) first coined the term 'low dosage of neuroleptic therapy' and reported five therapy-resistant patients with a diagnosis of BPD. Two patients responded to perphenazine (2–6 mg daily), two responded to thiothixene (in dosages up to 10 mg daily), and one responded to thioridazine (25 mg at night). These doses are considerably lower than those required for the treatment of schizophrenia and are also lower than the dosages reported when neuroleptics are used to treat depression (Robertson & Trimble, 1982). Brinkley *et al* (1979) commented that dosage titration was "a critical aspect of the use of neuroleptics in this population because the margin between the symptom free state and the onset of sedative side effects is fine".

Two American retrospective case-note studies (Soloff, 1981; Cole *et al*, 1984) provided further uncontrolled evidence that neuroleptics may benefit borderline subjects. In Soloff's (1981) study, 5 out of 11 (45%) cases of BPD had a good outcome, while Cole *et al* (1984) noted that 10 out of 17 (58%) BPD subjects did well on neuroleptics, although those with a co-existing schizophrenia-like illness or depression seemed to benefit most. In an open trial, Leone (1982) compared loxapine (a tricyclic antipsychotic drug) with chlorpromazine; loxapine reduced anger hostility somewhat more than chlorpromazine in the early phase of the trial, but by six weeks the drugs appeared to be equally effective. Side-effects, particularly drowsiness and various dyskinesias, resulted in poor compliance for both drugs and a high drop-out rate.

Most of the drug studies described above were drawn from private analytical practice, and therefore represent a very biased sample. Furthermore, the absence of placebo controls in these studies makes it difficult to estimate the magnitude (if any) of the reported drug effect.

One prominent symptom of BPD is a tendency to repeated overdoses. Of those attempting suicide, 48–65% have personality disorders (Philips, 1970; Ovenstone *et al*, 1973). Casey (1989) also reports a frequency of 65%, although Jacobson & Tribe (1972) report a rather lower prevalence. Prospective studies have demonstrated that social-work intervention (Oast & Zitrin, 1975) and intensive out-patient supervision (Chowdrey *et al*, 1973) do not reduce the frequency of subsequent suicidal behaviour. Montgomery & Montgomery (1982) compared the effects of 20 mg intramuscular flupenthixol monthly with placebo and 30 mg mianserin. They selected subjects who had twice attempted suicide, but had no concurrent axis I disorder. Most subjects had BPD (by DSM–III criteria (American Psychiatric Association, 1980)) but a few had histrionic or dependent personality disorders. For the first three months of the trial there were no differences between drug and placebo groups, but by six months the flupenthixol-treated group attempted suicide significantly fewer times than the placebo group. The parallel group treated with mianserin derived no benefit.

Serban & Siegel (1984) conducted a large prospective study on 52 consecutive patients with either DSM–III BPD or SPD or both, who presented to the Bellvue Walk in Clinic in New York. Thiothixene (mean dose 9.8 mg) and haloperidol (mean dose 3.0 mg) were compared in a parallel design, but the study lacked a placebo control group. Overall 56% of the patients showed marked improvement; 28% did moderately well; 12% showed no change; and one subject (2%) was worse. Symptoms improving most were cognitive disturbance, derealisation, ideas of reference, anxiety, and depression. One finding of particular interest was that 'low self-image' – a psychological symptom traditionally held to respond only to psychotherapy – improved

dramatically with both these neuroleptics. Thiothixene but not haloperidol resulted in an overall improvement on the Borderline Syndrome Index (Conte *et al*, 1980), suggesting that core borderline features may also change in response to drug therapy.

Although the majority of reports on the use of neuroleptics in BPD are favourable, Steiner *et al* (1979) describe an adverse reaction which they call 'behavioural toxicity'. They reported nine subjects with DSM-II borderline schizophrenia (DSM-II 295.5), although the limited case material provided in the text suggests that six had schizoid rather than schizotypal personality disorder, and three had pure BPD, but none were initially psychotic. In an attempt to treat their 'pre-schizophrenia' they were given 150–500 mg chlorpormazine or 7–12 mg haloperidol daily, and this resulted in the precipitation of psychotic symptoms and 'behavioural toxicity', characterised by psychomotor agitation, conceptual disorganisation, paranoid delusions, depersonalisation, and derealisation. There were no associated Parkinsonian or other extrapyramidal symptoms. The mechanism of this unusual reaction is uncertain and the authors postulated either a psychodynamic mechanism, or that the drugs precipitated an atropine-like psychosis.

Placebo-controlled trials of neuroleptics

In the first of these trials, Goldberg *et al* (1986) compared thiothixene with placebo in 50 patients. Subjects were recruited through an advertisement in a local newspaper outlining the main features of DSM-III BPD. Respondents were subsequently screened using the Structured Interview for Borderlines (Baron, 1981) and were only included if they fulfilled DSM-III criteria for BPD or SPD and had experienced the behaviour in question for at least three months. Patients who also had schizophrenia, mania, melancholia, or severe physical illness were excluded. Twenty-nine were women, 17 had BPD, 13 SPD and 20 had both SPD and BPD. Patients took a variable dosage of thiothixene in 2 mg and 5 mg tablets and were asked to titrate their own dosage up to a maximum of 40 mg daily. At the end of the trial the average dose of thiothixene taken was 8.67 mg while the average placebo dose was 26.36 mg. This difference, both large and significant, suggests that the drug was either more effective or produced more side-effects than placebo (or both). Large drug–placebo differences were demonstrated for delusions, ideas of reference, psychotic anger and hostility, phobic anxiety, and obsessive–compulsive symptoms. Rather smaller drug–placebo differences were present for somatisation, depersonalisation, derealisation, suspiciousness, and paranoia. There were negligible effects for hallucinations and depressive hostility and sensitivity to interpersonal rejection. 'Anger hostility' and sensitivity to interpersonal rejection showed a large placebo response, and because of this Goldberg *et al* (1986) suggested that the patients presenting with these symptoms might benefit more from psychotherapy than from drugs. Measurement of the 'personality cluster items', that is, borderline criteria and schizotypal criteria, showed large significant improvements over time for both placebo and the active drug, but there were no significant drug–placebo differences, and it is possible that the improvement in these measures was the result of psychotherapy after the drug trial.

In the second trial, Soloff *et al* (1986*a*) compared haloperidol (mean dosage 7.24 mg) with placebo and amitriptyline (mean dosage 147 mg). Because their subjects were an in-patient group they may have been rather more disturbed, yet at the same time more representative of hospital clinical populations and therefore more relevant to clinical practice than the community-based subjects studied by Goldberg *et al* (1986). All subjects were screened using the Diagnostic Interview for Borderlines: 43% had BPD, 6% SPD, and 51% both BPD and SPD. Haloperidol was superior to amitriptyline and there were large drug–placebo differences for haloperidol for a broad spectrum of neurotic and psychotic symptoms as well as measures of behavioural dyscontrol. Depression improved only according to the self-rated Beck Depression Inventory, not according to the observer-rated Hamilton Rating Scale for Depression. Haloperidol also led to a significant improvement in the Schizotypal Symptom Inventory, a scale purported to measure core features for schizotypal personality disorder.

The third placebo-controlled study is that of Cowdrey & Gardner (1988), and although only 16 subjects with pure BPD were examined, the study itself had an elegant design. Taking advantage of the chronicity of personality disorders, these authors repeatedly challenged their patients with four different drugs as well as placebo for consecutive six-week periods in a longitudinal crossover trial. The drugs tested were trifluoperazine (mean daily dose 7.8 mg), carbamazepine (820 mg daily), tranylcypromine (40 mg daily), alprazolam (4.7 mg daily), and placebo. Only 10 patients started the trifluoperazine trial and three dropped out in the first three weeks (two because of orthostatic hypotension and one because of extrapyramidal disorder), and a further two dropped out between three and six weeks, indicating that only 50% of the subjects were able to tolerate trifluoperazine. For those who completed the trial

there was significantly less tendency to suicide attempts and behavioural dyscontrol, although the improvement was less than with carbamazepine in the same patients. There were also modest improvements in depression, anxiety, and sensitivity to rejection. The results of the trial were complex, with each drug showing beneficial effects on different aspects of BPD. Only tranylcypromine was superior to placebo over a broad range of measures of self- and observer-rated mood changes and behavioural dyscontrol. Carbamazepine was superior to placebo for behavioural dyscontrol but not for measures of dysphoria. Alprazolam was significantly worse than placebo for behaviourial dyscontrol, although for 2 of the 16 subjects, alprazolam emerged as the best drug.

The studies by Goldberg *et al* (1986) and Soloff *et al* (1986*a*) are methodologically sound, incorporating sizeable numbers of subjects as well as placebo controls, and both show a broad spectrum of efficacy for neuroleptics over a wide range of both neurotic and psychotic symptoms in subjects with well defined BPD and SPD. They therefore confirm the earlier reports of the American psychoanalysts and the open studies reported from the UK, US, and Belgium. The more definite indication for neuroleptic use appears to be brief psychotic episodes and episodes of severe behavioural dyscontrol. Neuroleptics taken over a longer period may benefit a few subjects who previously derived some benefit during an acute episode of dyscontrol or psychosis. In general, the high-potency preparations, such as pimizode, thiothixene or trifluoperazine, in low dosage have been preferred because they lack sedative side-effects which are apparently much abhorred by these patients. However, some patients prefer small doses of the low-potency preparations such as thioridazine and chlorpromazine because these drugs are less prone to cause extrapyramidal reactions, while their sedative effects are often valued.

Tricyclic antidepressants in borderline subjects

The poor response to tricyclics among subjects with personality disorders was observed in one of the first open trials of imipramine. Klein & Fink (1962) identified 13 subjects with "histrionic labile affects and a manipulative character" who responded poorly. Kiloh *et al* (1962), in a discriminant-function analysis, also found that self-pity, irritability and hysterical features were associated with a poor response to imipramine. Paykel (1972) treated 85 women with depression and classified them according to the typology of Overall *et al* (1966) into psychotic depressives, anxious depressives, hostile depressives, and young depressives with personality disorders. Psychotic depressives did best, while 'anxious depressives' were least responsive. Deykin & Dimascio (1972) found the only items to show any predictive association with a positive tricyclic response were a stable occupational record and a previous history of a substance abuse. Shawcross & Tyrer (1985) examined 17 out-patients who failed to respond to either a tricyclic or a monoamine oxidase inhibitor (MAOI), and of these, 12 (70%) had a recognisable personality disorder.

The first prospective study of the tricyclics in subjects with personality disorders was conducted by Akiskal *et al* (1980). They recruited 65 patients with 'characterological depression' who had: (a) a history of mild depressive symptoms for five or more years, (b) onset before the age of 25 years, (c) depressive symptoms for most of the year, (d) a condition that did not represent the residuum of a well defined depressive episode requiring hospital admission. Treatment was initially with a tricyclic antidepressant with mainly noradrenergic properties (desimipramine or nortriptyline) in full dosage, and if this failed a serotonergic drug such as amitriptyline or clomipramine was prescribed also in full therapeutic dosage (150–200 mg daily). Out of the 65 subjects, 20 (31%) responded well to tricyclic therapy. Responsiveness was associated with: a history of major depression; hypersomnia; a mild hypomanic episode in response to tricyclics; and female sex. Non-responders were more often male and had an unstable personality and a history of abusing hypnotics, alcohol or psychostimulants; they also had a poorer social outcome.

In antidepressant studies where the primary aim is the treatment of depression rather than the personality disorder, tricyclics are less successful among those with co-existing personality disorders than among subjects who are free of personality disorders. Black *et al* (1988), in a retrospective case-note study, compared 75 subjects with major depression and co-existing personality disorder with 152 with pure major depression. Of those with pure depression, 64% responded well to adequate tricyclic treatment, compared with only 27% of those with personality disorder. This study has relevance for hospital-based practitioners because it was based on a large in-patient sample, and the difference between the two groups was both large and significant. Using a similar retrospective design, Pfohl *et al* (1984) also showed that the response to antidepressants (not specified as tricyclics) was worse among patients with personality disorder (16%) compared with patients with pure depression (50%). However, as the main outcome measure was made after only two weeks' treatment, these figures are unreliable and probably too pessimistic.

Surprisingly there is only one prospective, well controlled, double-blind trial in the literature which compares amitriptyline with placebo and haloperidol among subjects with properly diagnosed DSM–III BPD or SPD, some of whom also had major depression according to Research Diagnostic Criteria (Soloff *et al*, 1986*a*). As a group, the depressed subjects treated with amitriptyline did only marginally better on the Hamilton and the Beck scales than subjects receiving placebo, whereas patients on haloperidol did markedly better on these scales. However, more detailed scrutiny of individual cases showed that some patients treated with amitriptyline responded well, while others became much worse.

In another paper, possibly on the same subjects, Soloff *et al* (1986*b*) reported that the 13 amitriptyline responders improved on ratings of depressed mood and in many areas of impulsive behaviour, including temper tantrums, assaultive threats, and manipulative behaviour. But the 13 amitriptyline non-responders deteriorated progressively and by six weeks were far worse than the placebo group on measures of global functioning, paranoid ideation, and impulsive behaviour. Non-responders were also more demanding, expressed more suicidal threats, and made more physical assaults. Responders and non-responders had similar plasma tricyclic levels, and it is of note that the non-responders were not over-medicated, under-medicated, nor hypomanic. Because of this, Soloff *et al* (1986*b*) cautioned, "clinicians should be aware of the potential of paradoxical effects of tricyclics in borderline patients".

Similar paradoxical effects and rage reactions had also been observed many years previously among a group of emotionally unstable adolescents (Klein & Fink, 1962), and Rampling (1978) reported four depressed subjects who experienced severe aggressive outbursts within a few hours of taking a tricyclic. This generally poor response of BPD depression to tricyclic antidepressants may explain why they often prove to be disappointing among depressive in-patients, since more than half of the in-patients with unipolar depression also have personality disorders (Baxter *et al*, 1984).

Monoamine oxidase inhibitors

All three studies in the literature on the effects of MAOIs on the personality disorders report beneficial effects (Hedberg *et al*, 1971; Liebowitz & Klein, 1981; Cowdrey & Gardner, 1988). Hedberg *et al* (1971) examined 96 patients with a diagnosis of schizophrenia, but among the subjects there were 32 patients with pseudoneurotic schizophrenia, the probable forerunner of BPD. Half the patients with pseudoneurotic schizophrenia responded to tranylcypromine alone, 28% to trifluoperazine alone, and 22% to the combination. Prompted by this observation, Liebowitz & Klein (1981) gave phenelzine (mean dose 75 mg) to 16 women, aged between 18 and 45, who were bright and articulate and were all suffering from 'hysteroid dysphoria'. Fourteen of these 16 subjects also fulfilled DSM–III criteria for BPD. They also received twice-weekly dynamically orientated psychotherapy by experienced psychiatric social workers throughout the trial. Eleven of the 16 (68%) responded well to this combination of MAOIs and psychotherapy, but five failed to respond. Of these, two suffered from alcoholic relapses, one had to be admitted for worsening depression, and two dropped out because of side-effects, including delusional parasitosis. By the end of the open phase of the trial, the number of patients who continued to fulfil DSM–III criteria for BPD had fallen from 11 to 6. At the end of three months the 11 improved patients entered a double-blind placebo-controlled withdrawal study, and 8 (73%) relapsed, with an increasing frequency of physically self-damaging acts, feelings of emptiness and boredom, and the break up of relationships which had been going well during the open phase of the trial.

A third longitudinal crossover, placebo-controlled trial of MAOIs was conducted by Cowdrey & Gardner (1988) in 12 patients with DSM–III BPD. In this trial, patients with comorbid schizophrenia or manic or major depression were excluded, but those with lesser degrees of affective disturbance were included. Nine patients completed a trial on tranylcypromine and there was marked improvement for anxiety, depression, and sensitivity to rejection. Behavioural dyscontrol also improved but this was less impressive than for carbamazepine among the same patients. In studies where MAOIs have been used to treat depressive disorders, rather than the personality disorder itself, MAOIs emerge as less effective antidepressants among subjects with combined depression and personality disorder, than when used to treat depression uncomplicated by personality disorder. Shawcross & Tyrer (1985) in a study of depressed neurotic out-patients found 68% of the non-responders had a personality disorder (mainly anancastic and passive dependent) compared with only 18% of the phenelzine responders. There are divergent views as to whether the beneficial effects of MAOIs on the personality disorders are due to their antidepressant effects, as in cases of atypical depression (Cowdrey & Gardner, 1988), or whether it is their psychostimulant

properties that are of critical importance (Wender *et al*, 1981).

Electroconvulsive therapy

While the immediate response to ECT may be good, there is a high relapse rate among BPD subjects with depression. Zimmerman *et al* (1986) treated 25 patients who had major depression with ECT. Ten subjects also suffered from a variety of personality disorders, while the remaining 15 had major depression only. The short-term response to ECT was good in both groups, but by six-month follow-up, five out of the ten subjects with personality disorder had been readmitted compared with only one out of the 15 with pure depression. Kramer (1982) also reported five BPD subjects with depression: two showed little or no response to ECT, two had an equivocal response with rapid relapse, and only one had a good response, but this was also soon followed by relapse. In a retrospective study where the primary aim of the ECT was to treat depression, Black *et al* (1988) found that 11 out of 14 (79%) patients with pure major depression responded well to ECT, but the response rate for depression in the personality disorder group was similar at 75%. Using a similar design, Pfohl *et al* (1984) found that 65% of their patients with pure depression responded well to ECT compared with only 40% of those with depression and personality disorders. Possibly as a consequence of the poor response to ECT, this type of depression is less commonly treated with ECT; thus Black *et al* (1988) found that only 45% of patients with a combined diagnosis of major depression and personality disorder received ECT compared with 65% of those who had major depression alone. Figures in the study by Pfohl *et al* are lower but show a similar trend – 27% for pure major depression, and only 13% for depression combined with personality disorder.

However, ECT may be useful in certain instances. Firstly, anyone, regardless of their previous personality, may suffer a series of catastrophes and as a consequence develop a severe depressive illness which may respond to ECT. Secondly, Perry (1985) found that some BPD subjects experienced 'double depression' – discrete episodes of major depression superimposed on chronic dysphoria. During these phases, there is an abrupt and apparently inexplicable regression, and patients enter a phase of severe and frequent behaviour dyscontrol with daily or almost daily suicidal attempts and self-mutilation. ECT is often beneficial in breaking the cycle and stopping repetitive self-damaging acts. Even though the effect of ECT may be short lived, it can be life saving, while the extra time given may provide a breathing space, enabling the development of alternative treatment strategies.

Lithium

Cade's original discovery that lithium might be a cure for mania stemmed from his observation that lithium had a tranquillising effect on guinea pigs (Cade, 1949). A calming effect on the aggressive behaviour of other animal species such as Siamese fighting fish, and the territorial behaviour of hamsters, was also later demonstrated by Weischer (1969).

Only in the USA has it been possible to study the effect of lithium on the more seriously violent individuals found in prison populations (Sheard, 1971; Tupin *et al*, 1973; Sheard *et al*, 1976). Tupin *et al* (1973) studied 27 male convicts, approximately half of whom had personality disorders of a mainly explosive type, the remainder having schizophrenia; they all had a pattern of recurring, easily triggered violence. A high dose of lithium (1800 mg) was used, although the mean plasma level was only 0.82 mEq/l. Tupin *et al* (1973) commented that this group may handle lithium differently to the usual manic–depressive population, or alternatively be less cooperative about taking medication. Fifteen (56%) of their subjects showed a marked decrease in the number of prison infractions, 3 (11%) showed an increase, and 4 (14%) showed no change. Two patients became increasingly psychotic on lithium, presumably as a consequence of the high dosage and lithium toxicity. Many subjects reported an increased capacity to reflect, a frame of mind Monroe (1970) calls 'reflective delay', or as one convict aptly put it, "now I can think whether to hit him or not".

Sheard's first study was an open trial of lithium in 12 aggressive violent delinquents (mean age 19) from the Cheshire Correctional Institution in Connecticut. Serious aggressive episodes showed a much larger reduction with lithium than minor antisocial acts. However, a normal or high serum lithium level was a critical factor, the reduction in aggressive episodes only occurring if the level was above 0.6 mmol/l. Improvement for the whole group was largely accounted for by three (25%) subjects who appeared to be particularly responsive to lithium (Sheard, 1971).

In a second and much larger study, Sheard *et al* (1976) studied 66 subjects mainly with severe personality disorders who had been convicted of a serious aggressive crime, such as manslaughter, rape or assault, who continued to have chronic assaultive behaviour in prison. Improvement was measured objectively by counting the total number of major

and minor infractions of the institution's rules. Major infractions were assaults or serious threatening behaviour, and these were punished with time "in the hole" (the seclusion unit). Minor infractions were offences such as possession of contraband, or being out of place at the wrong time, and these were usually punished by a loss of recreational privileges. For the first month all subjects were drug free; then half the subjects took lithium while half took placebo for the next three months, and this was followed by a further drug-free period. The infraction rate was similar for the two groups during the first drug-free month. However, during lithium therapy the frequency of major infractions steadily declined to zero by three months, whereas subjects taking placebo continued to have a high rate (a significant difference). However, minor infractions showed little or no change in the treatment group, indicating that lithium did not cause a global inhibition of behaviour. On stopping the lithium there was an immediate rebound increase in the number of major infractions in the treatment group.

Lithium may also be useful in some mentally retarded subjects prone to aggressive episodes and self-mutilation. The cause of this behaviour is unknown but is presumably an admixture of brain damage and character pathology rather than affective disorder. Wickham & Reed (1987), pooling the results of three controlled trials (Worral *et al*, 1975; Tyrer *et al*, 1984; Craft *et al*, 1987), found an overall response rate of around 70–75% compared with a placebo response rate of 30% (Craft *et al*, 1987). Side-effects such as polydipsia and polyuria (Dostal & Zvolsky, 1970) and episodes of lithium toxicity (Worrall *et al*, 1975), probably secondary to unrecognised episodes of intercurrent illness such as diarrhoea, may limit the use of lithium in this population, while Craft *et al* (1987) also observed one or two subjects who became more aggressive while on lithium.

The only placebo-controlled study of lithium in the personality disorders was among a group of female adolescents with brief spontaneous mood swings of elation, depression, anger, and overtalkativeness who suffered from "the emotionally unstable character disorder" (Rifkin *et al*, 1972). In their six-week double-blind crossover trial, patients were randomly allocated to placebo or lithium. Of the 21 patients studied, 14 were judged to be better on lithium, four on placebo, and three showed no improvement. The only statistically significant change due to lithium was a decrease on 'within-day mood fluctuations'.

Lithium may also be helpful for a few alcoholics. Among attenders at an out-patient clinic with alcoholism there may be a high prevalence of personality disorders. Tyrer *et al* (1988) gave a figure of 69%, while Valgum & Valgum (1989) estimated that 30% of female alcoholics admitted to hospital had both BPD and SPD, which was ten times the rate in non-alcoholic female admissions. Dryud (1972) has suggested that alcohol and drug addictions may represent a form of self-medication to escape from the intolerable moods associated with BPD. Both Klein *et al* (1974) and Merry *et al* (1976) found lithium gave some benefit to clinic alcoholics, particularly where there was co-existing depression. Fawcett *et al* (1987) reported that 67% of detoxified alcoholics who took lithium remained abstinent for 12 months, compared with only 42% of controls, but these effects were independent of any previous depression.

Finally, Stone (1990) reported that around 8% of his large sample with DSM–III BPD developed affective disorder. A few suffered from bipolar II disorder, and some of these showed a gratifying response to lithium. There are thus reports that lithium can help small numbers of subjects with diverse personality disorders, such as emotionally unstable adolescents, some violent criminals, aggressive mentally retarded subjects, a few alcoholics, and a few borderline subjects who show bipolar features. In the absence of any useful clinical predictors, picking out the small minority of responders is almost impossible. Affective features and a family history of classic affective disorder may be useful indicators, while Goetzl (1977) and Eichelmann (1988) on the basis of single case histories suggest that a family history of alcoholism may also be relevant. In some cases a two-month therapeutic trial of lithium may be the only way of selecting lithium-responsive subjects from the large majority of non-responders.

Benzodiazepines

Benzodiazepines are contraindicated in personality disorder because of their propensity to disinhibit and to induce rage reactions and states of drug dependency. The early reports of chlordiazepoxide-induced rage reactions showed that these episodes were almost exclusively confined to subjects with 'pseudoneurotic schizophrenia' (Tobin *et al*, 1960). Many of the earlier, more favourable reports included mixtures of patients, some of whom had personality disorders, schizophrenia and epilepsy, and any beneficial effects on personality disorders were mixed with the known beneficial anti-epileptic effects of benzodiazepines.

Kalina (1964) studied 52 mainly male prison inmates with diagnoses of schizophrenia, schizoid personality disorders and epilepsy who were "constant sources

of friction and unrest with mainly hostile aggressive manifestation". Diazepam (20–30 mg daily) given for 6–12 months led to a complete resolution of symptoms of violence, destructiveness and belligerence in 33 (63%) of the subjects, while a further 3 (6%) were improved and 16 (31%) were unchanged. As might be expected, the diazepam helped the epilepsy and seven out of eight epileptics became seizure free. Diazepam reduced the symptom of interictal belligerence among a group of epileptic in-patients (Goddard & Lokare, 1970) while intramuscular diazepam (5–10 mg) reduced both fit frequency and aggressive outbursts. The drug had a "favourable effect improving some undesirable aspects of personality function".

Lion (1979) found that both oxazepam (120 mg daily) and chlordiazepoxide (100 mg daily) were superior to placebo in controlling episodes of aggression and temper among subjects with explosive personality disorders (none of whom had epilepsy) and that oxazepam was superior to chlordiazepoxide. Intramuscular lorazepam is also useful for the treatment of violent episodes among in-patients who have either psychotic or non-psychotic aggression (Bick & Hannah, 1986).

A more novel use of rapidly absorbed short-acting benzodiazepines is reported by Griffiths (1985). He described two patients with Monroe's episodic behavioural disorders (see below) who were able to abort their rage attacks by taking triazolam (0.5 mg) at the onset of their prodromal symptoms. In his first case a patient presented with a ten-year history of uncontrolled paroxysms of rage. Although these rage attacks were usually triggered by external events, the patient experienced a prodromal period of gradually escalating hallucinations, irritability, racing thoughts, loud speech, hyperactivity, and insomnia. Once the rage began, however, he experienced himself as a passive observer watching the destruction of a wall or the door of his car. Both triazolam (0.5 mg) and clorazepate (15 mg), administered during the prodromal phase, were able to abort these rages in 80% of instances, but a daily dosage of clorazepate proved ineffective. Because the triazolam was rapidly absorbed, peak levels were present only one hour after ingestion. In our own unit a man with BPD, alcoholism, depression and self-mutilation discovered himself that he could abort some episodes of self-mutilation by taking lorazepam (1 mg) sublingually as soon as he felt an episode of self-mutilation was imminent, as this markedly reduced his anxiety within 15 minutes. Eichelmann (1988) also reports a case of a 57-year-old man, prone to severe destructive rages, and fulfilling DSM-III criteria for intermittent explosive disorder who experienced a complete resolution of his rages by taking oxazepam.

Faltus (1984) reported three cases of BPD with histories of alcohol and substance abuse, multiple admission to hospital, and failure to respond to a variety of other drugs including tricyclics, neuroleptics and lithium who responded well to a small dose of alprazolam. Although the Cowdrey & Gardner (1988) trial in BPD subjects was mainly unfavourable to benzodiazepines, alprazolam emerged as the best drug for 2 out of their 16 (12%) well defined BPD subjects; it was superior to placebo, tranylcypromine, carbamazepine, and trifluoperazine. However 7 out of 12 (58%) of their patients taking alprazolam had serious episodes of dyscontrol, compared with only 2 out of the 13 (14%) taking placebo. Aggressive episodes on alprazolam were both more frequent and more severe. Thus one woman who had previously only shouted at her child threw a chair at him, while another who had never previously mutilated herself slashed her neck (Gardner & Cowdrey, 1985).

The prescription of benzodiazepines should therefore be confined to those with intermittent explosive disorder or the interictal personality disorder of temporal lobe epilepsy, although rapidly acting benzodiazepines may sometimes help abort episodes of dyscontrol. Occasional patients with BPD, particularly those with a history of drug and alcohol abuse who fail to respond to other regimes, may also respond. The main caveat to their use is their propensity to cause rage reactions, and some authorities such as Tyrer (1988) feel they are almost absolutely contraindicated because of this. Deitch & Jennings (1988) however have recently questioned this view and they quote a large controlled series where the prevalence of such rage reactions is found to be around 1% among subjects taking benzodiazepines and among placebo control groups.

Impulsiveness, episodic phenomena, and the anti-epileptics

The most seriously disruptive symptom of personality disorder is episodes of impulsive aggression. These take the form of rage reactions, assaults on others, self-mutilation, commonly wrist or body slashing, self-inflicted burns, and impulsive overdoses. Cowdrey & Gardner (1988) consider that the behavioural dyscontrol manifested by BPD subjects may represent one of the types of episodic disorder, as described by Monroe (1970, 1982). The episodic disorders according to Monroe are common, with the core feature being "an abrupt onset of intense mixed dysphoric effects". This abruptly appearing recurrent maladaptive behaviour interrupts the lifestyle or 'life flow' of the

individual. The content of this dysphoria varies according to the underlying illness: thus if dysphoria takes the form of panic attacks, the underlying illness is an anxiety neurosis; if it takes the form of a brief psychotic episode the underlying disorder is a functional psychosis; and if it is an attack of violence the underlying disorder may be psychopathy. The behaviour is not only out of character for the individual but also out of context when it occurs, and patients sometimes report a compulsion in such behaviour. Between these episodes there is a symptom-free interval when neither the patient nor relatives are able to offer any rational explanation for the behaviour but sometimes refer to these episodes as 'spells', 'attacks' or 'seizures', and so liken them to true epilepsy.

Even though Monroe (1970, 1982) does not believe that the episodic disorders are truly epileptic, there are often prodromal symptoms, particularly mounting anxiety, motor agitation, and sometimes even auras reminiscent of classic temporal lobe epilepsy such as light headedness, visual distortions, olfactory and other sensory phenomena. These prodromal symptoms are followed abruptly by a florid disturbance that is sometimes accompanied by mild confusion and disorientation. After the episode there is commonly much relief of tension and some satisfaction as well as tranquillity and partial amnesia for the episode itself. As with epilepsy, patients with episodic disorders can often predict the impending acute phase and may make frantic attempts to abort attacks. Common precipitating factors for these episodes of behavioural dyscontrol are small amounts of alcohol or drugs which would have little effect on most individuals, irregular eating and sleeping habits, psychological stress, physical exhaustion, and excessive sensory stimulation.

Despite some resemblance between the symptoms of BPD and those of temporal lobe epilepsy, the changes on electroencephalography (EEG) in temporal lobe epilepsy are uncommon in BPD. Cowdrey *et al* (1985) examined the EEG changes in 39 subjects with BPD and found only one subject with atypical temporal lobe spike and wave activity, and a further three with some focal abnormalities in the temporal lobe, although there was an increased rate of non-focal posterior spike and wave activity in comparison with a control group of unipolar depressives. Androlunis *et al* (1982) found no difference in the prevalence of abnormal EEGs between their BPD and schizophrenic subjects, nor was there an increased rate of EEG abnormalities among their 'organic borderline' subgroup. However, abnormal slow-wave activity followed by bursts of fast-wave activity was reported in 38% of BPD subjects in another study (Cowdrey *et al*, 1985). Similar diffuse non-focal slow-wave activity has also been reported among subjects incarcerated for recurrent violence and among some recurrently suicidal individuals, and this pattern has been referred to as an immature EEG (see Cowdrey *et al*, 1985).

Resnick (1967) was the first to report some benefit for diphenylhydantoin among a group of disruptive prisoners and some improvement in academic and social performance among a few impulsive hyperactive delinquents. Sadly, this early optimistic report was not replicated by Lefkowicz (1969), who conducted a more rigorous placebo-controlled trial in 50 "disruptive delinquents". In his study, staff ratings for disruptive behaviour fell by 40% for those taking placebo, but only by 26% for those taking diphenylhydantoin. There was even a suggestion that diphenylhydantoin made some individuals rather worse when compared with placebo, particularly on measures of distress, unhappiness, negativism, and aggressiveness. This very large placebo effect is consistent with Beecher's (1955) original figure of a 35% response rate to placebo in 15 studies on diverse medical conditions. The high placebo response rate suggests that drug trials on the personality disorders which lack a placebo control group may be meaningless.

A similar, equally negative finding for diphenylhydantoin was reported from the placebo crossover trial of Rosenblatt *et al* (1976) among a group of child-abusing parents. Diphenylhydantoin had beneficial effects only on anxiety, depression and somatic symptoms, but there was no improvement for the core symptoms of aggressiveness, impulsivity, or hostility.

The first description of the successful use of carbamazepine in episodic behavioural dyscontrol is probably the remarkable case described by Tunks & Dermer (1977). Their patient had congenital rubella and severe aggressive behaviour at the age of 10, resulting in admission at 13. She remained in hospital for the next ten years. A severe aggressive episode occurred every four days and 12–24 hours before the episode she would develop a glazed fixed expression in her eyes. Head-banging, scratching, and biting then followed. She failed to respond to phenothiazines, benzodiazepines, antidepressants, primidone, and oral contraceptives, but 800 mg carbamazepine daily (blood level 14 mg/l) led to a complete resolution of the disorder. Reducing the dosage led to a recurrence of episodes, and Tunks & Dermer concluded that a higher plasma level of carbamazepine was required for the control of episodic dyscontrol than for the control of epilepsy.

The realisation that carbamazepine may be an important psychotropic drug, as well as a useful

anti-epileptic agent, started with the demonstration by Okuma *et al* (1981) of its anti-manic effects. Other workers soon found that the addition of carbamazepine to lithium could prevent relapse among lithium-resistant manic–depressives (Ballenger & Post, 1980). Furthermore, the addition of carbamazepine to chlorpromazine led to a dramatic reduction in the frequency of violent episodes among schizophrenics in a high-security hospital (Hakola & Laulumaa, 1982) and when combined with haloperidol, resulted in better control for schizophrenic excitement (Klein *et al*, 1983).

The first placebo-controlled trial of the effect of carbamazepine on behavioural dyscontrol was by Neppe (1983) among a group of treatment-resistant, long-stay, mainly schizophrenic, in-patients. Out of 15 patients, nine improved on carbamazepine but only one improved on placebo. Carbamazepine reduced the severity of overt aggression by half, and the frequency of aggressive outbursts was decreased by two-thirds. Luchens (1984) carried out a similar six-week placebo-controlled crossover trial among seven violent patients (six with schizophrenia, one with personality disorder) and found the frequency of aggressive acts was decreased by 67% during the carbamazepine trial. He replicated these findings in a second series, of eight patients, five of whom had a normal EEG while three had an abnormal EEG. There was no significant EEG effect on the frequency of either verbal or physical aggression. The presence of an abnormal EEG was however associated with carbamazepine therapy leading to a greater reduction in the use of medication 'as required' (p.r.n.). Mattes (1984) also reports a beneficial effect for carbamazepine on aggression which was independent of EEG status and neuropsychological measures of organicity. He treated 34 subjects with heterogeneous psychiatric diagnoses, many of whom had personality disorders and all of whom suffered from aggressive outbursts, with carbamazepine (200 mg three times daily) for two to three months. On a rating scale of 0–4 (4 = severe physical assaults) the patients' average score of 2.56 at base line fell to only 0.35 at discharge.

The most relevant study on the effect of carbamazepine on behavioural dyscontrol among the personality disorders is that of Gardner & Cowdrey (1986). They conducted a six-week double-blind crossover trial of carbamazepine (200 mg three times daily) in 14 women with pure BPD, and a history of severe behavioural dyscontrol. Eleven of the placebo trials had to be discontinued because of clinical deterioration, compared with only one out of 14 carbamazepine trials. Seven (63%) patients while on placebo had episodes of severe major dyscontrol compared with only one (9%) on carbamazepine. Aggressive episodes during the carbamazepine trials were relatively minor, usually verbal outbursts only. Promising as this result appeared, it was not without its price: one subject developed psychotic depression and four others developed allergic skin reactions, leading to discontinuation of the drug in two cases. In both these cases substitution with diphenylhydantoin failed to show the same beneficial effect. Both Neppe (1983) and Gardner & Cowdrey (1986) commented that carbamazepine appeared to induce a state of 'reflective delay', permitting patients to contemplate their actions, rather than acting immediately on their impulses.

Adult attention deficit disorder and the psychostimulants

Follow-up studies of hyperactive children during adolescence have shown these individuals are often impulsive, disorganised, or may have a poor self-image, and up to a quarter may be delinquent (Weiss *et al*, 1979). Men with minimal brain dysfunction are more sociopathic and assaultive, while women tend to depression, promiscuity, and suicidal gestures, and the most frequent adult diagnoses are immature and impulsive personality disorders rather than the functional psychoses. Family and cross-fostering studies have indicated a possible genetic link between attention deficit disorder and childhood and adult personality disorders, particularly alcoholism, sociopathy, and hysteria (Morrison & Stewart, 1971; Cantwell, 1972).

Hill (1944) was the first to use amphetamines in the personality disorders, in eight patients with a history of hyperactivity in childhood, enuresis, deep sleep, and abnormal EEGs. "The personalities which responded are those showing an aggressive bad temper and a generally hostile tendency. . . . The most satisfactory patients are those predominantly aggressive characters who are capable of making interpersonal relationships but continually wrecking such relationships" (Hill, 1944). These drugs, with their propensity to addiction and to trigger paranoid psychoses (Connell, 1958), rapidly fell into disrepute and their use nowadays is confined to the rare disorder of narcolepsy and as aids to slimming.

Attempts to revive the use of psychostimulants in the treatment of adults with unstable temperaments and personality disorders were investigated by Wood *et al* (1976). In their first study, methylphenidate (up to 60 mg daily) was compared with placebo in subjects with adult impulsive disorders and a history of childhood hyperactivity. There were significant drug–placebo differences for tension, concentration

and temper but not for depression. In the second study, Wender *et al* (1981) also showed that pemoline (37.5–150 mg) was superior to placebo for concentration, temper, impulsivity and stress intolerance, but these effects were confined to subjects with a history of severe childhood hyperactivity. Mattes *et al* (1984) failed to discern much benefit for methylphenidate among these adults, but Shekim *et al* (1989) found that nomifensine was sometimes of great benefit. Even though nomifensine has now been withdrawn, because of fatal liver complications, it is of interest that it inhibits the reuptake of noradrenalin and dopamine, an action it shares with amphetamine.

Just occasionally a severely violent patient may show a dramatic sedative response to d-amphetamine. Richmond *et al* (1978) described a 30-year-old man with severe recurrent bouts of aggression, including hurling a carton of condemned dynamite across a motorway, and at other times karate-chopping his wife in the neck. The patient had a history of childhood hyperactivity; his father and two brothers were "always on a short fuse", while his own daughter was maintained on d-amphetamine. His marriage was described as good in terms of their "dynamite sexual relationship". Computerised tomography and sleep EEGs with sphenoidal leads were all normal. All his symptoms resolved with 20 mg d-amphetamine twice daily. The patient commented "this stuff makes me orderly. I can take things one at a time or if something is bothering me I can lay it aside and put it on the shelf. The only problem is the stuff makes me put on weight".

The amphetamine-responsive patients described almost 50 years ago by Hill (1944) seem to differ little clinically from the MAOI-responsive borderlines described by Cowdrey & Gardner (1988), except that Hill's patients were male and were labelled as psychopaths. Childhood hyperactivity was a common predictor for treatment responsiveness for both groups. There may be some overlap between subjects responsive to amphetamine and MAOIs. Thus Klein *et al* (1980) were able to switch some long-standing amphetamine users to MAOIs. Amphetamine responsiveness can be predicted formally by amphetamine testing, or more informally from the history of drug abuse. Mattes (1984) reported that such a history was the only useful predictor for a successful response to methylphenidate in adults, while Deykin & DiMascio (1972), but not Akiskal *et al* (1980), found it also predicted a responsiveness to tricyclics. Amphetamine testing predicts a successful response to pimozide in schizophrenia (Van Kammen *et al*, 1982) and, in depression, responsiveness to both imipramine (Fawcett & Siomopouloo, 1971; Van Kammen & Murphy, 1979) and to lithium (Van Kammen & Murphy, 1979). Amphetamine testing consists of measuring the effect of 30 mg d-amphetamine daily on mood-sensitive scales. In Fawcett's study three consecutive days on amphetamine were compared with three days on placebo, but in Van Kammen's study two days on d-amphetamine separated by at least two days on placebo were compared with the mean mood changes over four days of taking placebo. A significant alleviation of mood due to amphetamine was taken as a positive response. An assessment of the predictive power of amphetamine testing in BPD subjects might enable MAOI, amphetamine, or possible drug-responsive subjects to be more accurately identified at an earlier stage than is presently feasible.

Drugs and psychotherapy combined

Paykel (1989) graphically describes the debate that rages between the advocates of drugs and those who believe in psychotherapy in the treatment of depression. Historically, drugs and psychotherapy have often been diametrically opposed, with the proponents of each treatment arguing that the other was at best limited, and at worst harmful. Each camp was opposed to combined therapy, drug therapists arguing that psychotherapy aroused feelings that made patients worse, while psychotherapists suggested that drugs would fixate patients on somatic issues.

In the area of the personality disorders this debate has been far less acrimonious and combined therapies have been used for a long time. Possibly the high spontaneous remission rates in uncomplicated depression afford therapists the luxury of the belief that their particular therapy has been curative. However, among the personality disorders spontaneous remission in the short term is unusual and the response to both drugs and psychotherapy is meagre. Because of this therapists who favour one treatment approach are more willing to adopt the techniques of the opposite camp when indicated. Kernberg (1986), a leading authority on the pyschotherapeutic treatment of BPD, when considering the issue of suicide, writes "in all cases the treatment of the psychotic syndrome takes precedence over the treatment of underlying personality disorder, at least brief hospitalisation, possibly electroconvulsive treatment, may be required". By contrast Cowdrey & Gardner (1988), both psychopharmacologists, permitted patients to take part in their drug trial only on the precondition that they continued to attend their psychotherapist.

A survey of American psychotherapists with an interest in psychotherapy for BPD showed that

successful therapy was often two or three times weekly extending over four years (Waldinger & Gunderson, 1984). In addition, Gunderson (1984) writes that psychotherapists should have special attributes to treat BPD subjects, which include "a comfort with aggression, sensitivity to separation experiences, a sense of adventurousness and clarity of conceptual organisation". Perhaps these qualities or at least a generally tolerant attitude are also required even for those psychiatrists who adopt a mainly pharmacological approach. Possibly they should also be prepared to continue to see their patients for perhaps some three to six years, albeit at a rather lesser intensity than their more psychotherapeutically minded colleagues.

Although the majority of psychotherapists dislike the use of drugs, most will employ physical treatments for the more definite indications of suicide, severe behavioural dyscontrol, violent mood swings, and brief psychoses. Rather more controversial is their longer-term use as an adjuvant to psychotherapy. There are, however, two valid reasons why drug therapy can be viewed favourably in such circumstances. First, psychotherapy with BPD is associated with a drop-out rate of around 60% over six months (Gunderson *et al*, 1989) and some of this early drop-out may be prevented by concomitant drug therapy. Soloff (1987) puts the case even more strongly, and suggests that since drug trials have shown a consistent beneficial effect of small doses of neuroleptics, such treatments should be offered much earlier than after years of failure in psychotherapy. A second reason for favouring adjuvant drug therapy is the sheer expense of prolonged analytical psychotherapy which, as Gelenberg (1987) points out, puts it beyond the reach of all but the most wealthy. Supportive psychotherapy, once weekly, combined with a drug to help alleviate dysphoria, is more affordable and therefore may be made more widely available.

Prescribing for borderline subjects

All authors who write on the subject (Sweeney, 1987; Cowdrey, 1987; Soloff, 1987) acknowledge there may be special psychological difficulties in prescribing drugs for BPD subjects which are quite distinct from the well known pharmacological side-effects of the drugs. Thus medication is sometimes used as another medium for acting out in therapy, while histrionic patients may grossly exaggerate side-effects and this may lead to the premature cessation of pharmacotherapy. Sweeney (1987) describes how some patients have a strong anti-medication bias before any treatment. The prescription of medication is experienced unconsciously as the doctor's attempt to take control. To surmount this, both Sweeney (1987) and Gunderson (1987) advocate that prescribing should only be done in the context of a good therapeutic alliance, where both the doctor and patient act jointly as colleagues in a trial of the drug, with the patient assuming some control over dosage and the time of day to take the drug. This manoeuvre may help dispel fantasies of medical omnipotence and so diminish anti-authoritarian feelings and the tendency to act out.

Gunderson (1986) also highlights the clinging dependency of many BPD subjects who have underlying fears of abandonment. They may either fail to recognise or deliberately deny that a particular treatment has been helpful because to make such an admission could result in the termination of therapy. Also the addition of any new treatment, whether a different therapist, a new group, or a new drug, may be experienced by a borderline with marked rejection sensitivity as an intense negative event and result in a relapse. Drug treatment, like psychotherapy, for the borderline is difficult to conduct and often has a poor outcome and should not be embarked on lightly, as many patients may do well without drugs while others may be worsened by medication. Response rates to the drugs are far worse than in the functional psychoses, yet some patients may derive a modest benefit, although for a few subjects the relief may be striking. However, there should be no unrealistic expectation that drugs can alter any ingrained character traits or in some way compensate for childhood abuse or deprivation, which is common among BPD subjects (Stone, 1990).

Caution is required when prescribing for BPD subjects with suicidal tendencies. The lethality of the drug in overdose should be an important consideration in drug selection. Often it is better to avoid prescribing drugs at all, but if a drug has to be used then a benzodiazepine or neuroleptic is relatively safe in overdose. Winkleman (1975) recommends chlorpromazine for those "who are prone to take handfuls of tablets at random". Montgomery & Montgomery (1982) have demonstrated that flupenthixol injections can reduce the frequency of such overdoses. Tricyclics and MAOIs are moderately lethal drugs in overdose and so they should be used sparingly among these subjects. Lithium is highly lethal in overdose and among those who take repeated overdoses, it may be contraindicated, except possibly as a trial during an admission.

Conclusions and future research

Only a decade ago Soloff (1981) commented that even though drugs were commonly prescribed for

BPD there were no published guidelines for their use. Our knowledge and skill in prescribing has improved since then, not because any marvellous new drugs have been discovered, but more as a result of better diagnostic methods and a few well designated placebo-controlled trials. There is now reasonable evidence that many cases of BPD may respond to small doses of neuroleptics. Thiothixene, haloperidol and trifluoperazine have been shown to be superior to placebo, while perphenazine and thioridazine emerge favourably in open studies. These drugs seem to help a wide spectrum of symptoms including hostility, anger, suspiciousness, anxiety, depressed mood, delusions, behavioural dyscontrol, suicidal tendencies and sensitivity to rejection in cases of BPD. A rather more controversial area relates to their prolonged use as an adjunct to psychotherapy. Three studies suggest that MAOIs may also benefit a broad spectrum of symptoms in BPD subjects, but dietary restrictions and their risks with alcohol and in overdose may restrict their use. What limited information there is on pure SPD also suggests that neuroleptics may help in some cases (Goldberg *et al*, 1986) and a trial of low doses of neuroleptics may be indicated (Cowdrey, 1987).

Psychotic episodes in BPD respond well to brief admissions, often without the use of drugs, but when drugs are prescribed, neuroleptics are indicated. The doses required for the psychotic episodes of BPD are usually considerably lower than those used in the treatment of schizophrenia and there is a suggestion that higher doses may actually make some patients worse. When a psychotic episode has responded well to a particular drug the individual patient may also benefit from taking a smaller dose of the same drug for longer.

Behavioural dyscontrol is undoubtedly the most serious management problem posed by subjects with BPD and in these cases pharmacotherapy should be combined with some form of psychotherapy and, if necessary, institutional care. In some cases, a strong manipulative element is present, and the wish to control staff or relatives is obvious; in these instances psychotherapy may play a more pivotal role. However, most subjects with BPD who mutilate themselves do so on their own, and repeatedly, as a means of relieving intolerable states of inner tension.

Drug trials have shown that the neuroleptics and to a lesser extent benzodiazepines can help some patients, and these drugs should certainly be given a trial first, before moving on to the more potent, but medically more dangerous drugs, carbamazepine and lithium. Carbamazepine may be specifically useful in the dyscontrol of BPD (Cowdrey & Gardner, 1988) even in the absence of EEG or psychometric evidence of organicity (Mattes, 1984). There are as yet no trials of lithium in the behavioural dyscontrol of BPD but empirically a few cases may respond. Useful pointers to lithium responsiveness include mood disturbance, aggressive behaviour in the context of anger, a family history of classic affective disorder, and a personal or family history of alcoholism. Patients with serious episodes of aggressive behaviour extending over years should be given the benefit of a three-month trial of lithium (Sheard *et al*, 1976).

Depression and other mood disorders are common in the personality disorders. Thus classic DSM-III-R axis I syndromes, such as major depression, may sometimes respond to a tricyclic, although the response of major depression to tricyclics, MAOIs and ECT in BPD subjects is often equivocal and certainly much worse than in major depression uncomplicated by BPD. Panic disorder is also common and because panic attacks can sometimes act as a trigger for episodes of behavioural dyscontrol it is worth trying to treat. The mood disorders most characteristically associated with BPD are feelings of emptiness, boredom and frustration. This type of dysphoria usually responds poorly to drugs, but if drug therapy is attempted neuroleptics and MAOIs may be of more use than the tricyclics.

Attempts to subdivide the borderline syndrome into different subsyndromes, each responding to a particular drug, have not proved to be of much clinical value. A subgroup with spontaneously occurring mood swings, termed 'subaffectives' by Akiskal *et al* (1989) or 'emotional unstable character disorders'' by Rifkin *et al* (1972), may respond to lithium. In contrast, another subgroup where mood changes only occur in response to external stress, the 'hysteroid dysphorics', may do well with MAOIs (Liebowitz & Klein, 1981). Androlunis *et al* (1982) subdivided the borderline syndrome into organic and functional subtypes. They found that 38% of their sample had a significant organic contribution such as a previous head injury, epilepsy, encephalitis or a history of childhood attentional deficit disorder. Organic borderlines were more often male, had a younger age of onset and presentation, and more often had a family history of alcohol or drug abuse. The non-organic borderline was more commonly female, tended to breakdown in the later school years, with depression, or brief psychotic episodes, and more often had a family history of affective disorder. Androlunis *et al* (1982) recommend that organic borderlines should be treated in a structured environment with psychostimulants and anti-epileptics, whereas non-organic borderlines allegedly do better with psychotherapy, antidepressants, neuroleptics, or lithium. Ellison & Adler (1984) provide a neat but

also unvalidated formulation that divides borderline personality disorder into four subgroups: schizophrenic, affective, organic, and a true personality disorder group. Remedies appropriate to the axis I disorders should be applied, while the personality disorder subtype, that is those patients who lack any co-morbid axis I disorder, should be treated by psychotherapy alone.

Most of the subdivisions described above have little proven clinical usefulness, but the drug trial of Cowdrey & Gardner (1988) in BPD, covering trifluoperazine, MAOIs, carbamazepine and alprazolam, led to two important clinical observations, the one helpful, the second less so: most of the subjects with BPD responded to one or other of the trial drugs; however, there were no useful clinical predictors in the patient's history as to which drug might be helpful, with the possible exception of a history of childhood hyperactivity and MAOI responsiveness. A pragmatic approach may therefore be the best, with patients being offered two or three drugs in a sequential trial in the hope that one drug will be found that is both beneficial and well tolerated.

When conducting such a therapeutic trial the clinician should always watch for drug-induced clinical deterioration as well as the more common medical side-effects. The following types of drug-induced deterioration are described: increased behavioural dyscontrol, or paradoxical rage reactions, with benzodiazepines (Gardner & Cowdrey, 1985) and also with tricyclic antidepressants (Soloff, 1986*b*); severe depression with both propanolol and carbamazepine (Gardner & Cowdrey, 1986); increased psychoses and 'behavioural toxicity' with neuroleptics (Steiner *et al*, 1979); and increased aggression with lithium (Tupin *et al*, 1973; Craft *et al*, 1987).

The scientific study of even the most common psychotropic agents in the personality disorders is still in its infancy, but this is hardly surprising considering the enormous difficulties in treating even a single patient with BPD in a clinical let alone a research setting. As well as the clinical problems of therapy there are numerous theoretical difficulties in the design of trials with such unpredictable individuals; how subjects should be recruited; how the diagnosis is made; how long trials should last; as well as the ethical issues concerning the use of placebo and other treatments such as psychotherapy. Hitherto, subject recruitment for drug studies in the personality disorders has been haphazard and biased. Many of the earlier reports of beneficial drug effects came from private analytical practice, while in one study subjects with mild disorders were recruited from the general public through newspaper advertisements (Goldberg *et al*, 1986). At the other extreme, subjects with rare but extremely severe disorders have been studied in high-security institutions (Sheard *et al*, 1976). Information derived from these rather esoteric samples may not be applicable to the general population with personality disorders in hospital. Yet the most important clinical population that psychiatrists need to know about are those BPD subjects who are admitted because it is this group who will receive medication in clinical practice. So far there is only one trial which specifically examines "a consecutive series of subjects hospitalised for BPD or SPD" (Serban & Siegel, 1984).

The advent of DSM–III has greatly simplified the diagnostic problem and a number of interviews are now available which will yield a DSM–III diagnosis of BPD or SPD (see Tyrer, 1988). Because personality disorders have such a pleomorphic pattern of symptoms, several areas of psychopathology need to be monitored during a trial. Both observer-rating and self-rating methods may be necessary, because unless a drug provides some relief for 'self-rated dysphoria' it is unlikely to be taken for long. On the other hand, behavioural dyscontrol is best measured objectively by counting the frequency and severity of episodes rather than attempting to measure a subjective state such as impulsivity or aggressiveness. A wide variety of other affective, cognitive and psychotic symptoms should also be followed throughout the trial. Finally, there needs to be some measure of the personality disorder core itself, to see if this improves during the trial, and a number of new rating scales, based on DSM–III–R definitions of BPD and SPD, are now available.

The era of uncontrolled studies has passed, and only placebo-controlled trials should now be undertaken. Placebo effects in psychiatric patients are large, and subjects with personality disorders are often highly suggestible and may show rapid improvements without any specific therapy. The incorporation of placebos into these trials is essential, particularly if small beneficial drug effects are not to be missed. The use of placebo controls in two recent drug trials also enabled two types of drug-induced clinical deterioration, which might well have been missed, to be detected early: both amitriptyline (Soloff *et al*, 1986*b*) and alprazolam (Gardner & Cowdrey, 1988) triggered an increased frequency of rage attacks in comparison with placebo. The duration of drug trials in the personality disorders needs to be considerably longer than in the standard antidepressant drug trial. Thus maximal beneficial effects were not observed for three months in a trial of pimozide (Collard, 1976) or for lithium in aggression (Sheard *et al*, 1976). Although drug trials on the personality disorders may be difficult to

conduct, time-consuming, and expensive, funding bodies should view them favourably because of their clinical importance. Once acceptable protocols for these trials have been devised, newer drugs and other non-pharmacological remedies can be subjected to proper scientific scrutiny and so hasten the search for a cure for these debilitating disorders.

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