Psychological Medicine, 1998, **28**, 1169–1178. Printed in the United Kingdom

Antidepressant agents: from tricyclics to serotonin uptake inhibitors

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ABSTRACT

Background. The number of antidepressant drugs available in the market has grown rapidly in the last few years. The present paper underlines some of the pre-clinical and clinical problems that call close attention from the regulatory authorities when approving new drugs.

Methods. We present here a review of the literature.

Results. A wide heterogeneity in the action of the various antidepressants precludes any single theory about the pathogenesis and therapy of depression. Antidepressant activity, in fact, may be achieved by acting on a number of different monoaminergic mechanisms. The variety in the neurochemical effects of antidepressants is not reflected in clinical trials, which tend to stereotypy. In many cases clinical trials aim at demonstrating equivalence rather than differences in efficacy. Regulatory authorities should, therefore, pay attention in accepting the equivalence of effects of a new drug in relation to a reference one: most clinical trials of new antidepressant drugs do not have the power to detect clinically relevant differences.

Conclusions. Unconventional new pre-clinical tests are needed to generate antidepressants with a different mechanism of action. Clinical studies are needed to promote objective comparative evaluation of the cost, benefits and toxic effects of new antidepressants.

INTRODUCTION

A large variety of antidepressant agents (AD) are available today. Their market is still growing so they fulfil an apparent need for treatment. Antidepressant activity was first recognized in patients and only later were experimental tests developed in animals to mimic the clinical effects. Therefore, most of the pre-clinical tests used to screen antidepressant activity were tailored on the first drug. Thus, it is not surprising that most AD are repetitive in their mechanism of action and in many cases deserve the reputation of 'me-too drugs'.

The aim of this paper, which can be considered as follow-up of a preceeding paper (Garattini & Samanin, 1988), is not to review the whole field but to highlight some of the pre-clinical and clinical problems that call for close attention from the regulatory authorities. Since in most countries AD are partially or totally reimbursed by national health systems or similar organizations, questions related to the risk–benefit and cost–benefit relationships have also been taken into consideration.

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PRE-CLINICAL STUDIES

Acute effect

The first drug available was imipramine, synthesized by Hafliger and Shindler in the 1940s, as part of a series of antihistamines, sedatives and analgesics. In 1960 it was shown that imipramine tested in rats treated with reserpine, a monoamine depleting agent thought to induce depression in man, reversed some of reserpine's effects (hypothermia and bradycardia), and blocked ptosis and diarrhoea. This test had some selectivity for predicting antidepressant

effect, since chlorpromazine did not have similar effects (Costa *et al*. 1960).

Various compounds have subsequently been developed, mostly 'me-too drugs' with similar structures. Currently, a long list of tricyclic antidepressants (TCA) is available on the world market. Some recent AD cause selective serotonin reuptake inhibition (SSRI). At the present time several tests are used to predict the antidepressant effect of drugs, besides the original test with reserpine. Some AD produce subsensitivity to the hypothermic effects of clonidine, or antagonize apomorphine hypothermia, others potentiate the action of yohimbine. There are behavioural tests such as maternal separation in primates, canine puppies, guinea pigs and chicks, or peer separation in monkeys, as well as learned helplessness and behavioural despair, which are based on different constraining conditions with no possibility of escape.

While these tests were being developed, Glowinski & Axelrod (1964) showed that imipramine enhanced the activity of noradrenaline (NA) by blocking its reuptake by nerve endings, leading to an increase in its concentration at receptor sites. This inhibitory effect on uptake was not limited to noradrenaline. Certain TCA also caused a blockade of serotonin (5HT) and – though usually to a lesser extent – dopamine (DA) uptake. Therefore, by blocking monoamine uptake, AD raise their concentrations at receptor sites.

AD may differ not only in their action on monoamines but also with regard to the fact that uptake inhibition *in vivo* does not result in similar rises of extracellular monoamines in all brain regions. For instance, sertraline, a selective inhibitor of 5HT uptake, increased extracellular 5HT concentrations, measured by microdialysis, in the rat diencephalon (Rutter & Auerbach, 1993), but not in the frontal cortex (Invernizzi *et al*. 1995). Citalopram causes a steep rise in extracellular 5HT in the dorsal hippocampus (Invernizzi *et al*. 1995) but has little or no effect on dialysate 5HT in the frontal cortex (Invernizzi *et al*. 1992). Fluoxetine raises extracellular 5HT in the hippocampus and striatum, while desipramine is active only in the striatum (Kreiss & Lucki, 1995). Clomipramine has different effects in raphe nuclei and cortex (Adell & Artigas, 1991). This must be emphasized because a different regional increase of one monoamine induced by a particular AD results in different stimulation of receptors, and also because the density of monoamine receptor subtypes varies in different brain regions.

These brief considerations on the biochemical mechanisms of AD indicate the difficulty of formulating a unifying hypothesis on their acute effect (Garattini & Samanin, 1988).

Chronic effect

AD do not exert their clinical effects after a single dose; they require at least several weeks of treatment. Therefore, there was considerable interest in identifying the neurochemical effects of AD after chronic treatment.

The well-known down-regulation in β-adrenoceptor activity is usually caused by a reduction in the number of binding sites for [^{3}H]-dihydroalprendol or by a decreased response of β-adrenoceptors in the production of cyclic-adenosine monophosphate (c-AMP) when stimulated by suitable agonists (Vetulani *et al*. 1976; Banerjee *et al*. 1977; Wolfe *et al*. 1978; Bergstrom & Kellar, 1979). It should be stressed that the decrease in β-adrenoceptors is controversial with SSRI. There are findings in favour and against this effect for fluoxetine and fluvoxamine (for review see Johnson, 1991) whereas sertraline has been consistently shown to down-regulate β-adrenoceptors (Koe *et al*. 1983, 1987; Byerley *et al*. 1987). However paroxetine, the most powerful SSRI, did not reduce either the number of β_1- or β_2-adrenoceptors or the increase in c-AMP induced by β-adrenoceptor agonists (Nelson *et al*. 1989, 1990; Pratt & Bowery, 1990).

Decrease in the density of $5HT_2$ receptors

This decrease induced by repeated treatment with several TCA is well established (de Montigny & Aghajanian, 1978; Peroutka & Snyder, 1980) whereas results with SSRI are controversial. For paroxetine, citalopram, fluoxetine, fluvoxamine and sertraline there are positive results, i.e. reduction of $5HT_2$ density, as well as negative ones (for review see Johnson, 1991). However, $5HT_2$ receptors may be decreased either in number of functionally (desensitization). Sanders-Bush *et al*. (1989) showed that repeated treatment with sertraline and amitriptyline reduced the 5HT-stimulated hydrolysis of

phosphoinositides in rat cortex but only amitriptyline reduced the $5HT_2$ receptor binding sites.

The study by de Montigny and colleagues demonstrated that repeated treatment with AD of the SSRI class increases 5HT neurotransmission through the desensitization of somatodendritic $5HT_{1A}$ autoreceptors (Blier & de Montigny, 1994). This effect is accompanied by desensitization of terminal 5HT autoreceptors (Blier *et al*. 1990), which allows an increase in the 5HT, as shown by the fact that blockade of 5HT autoreceptors leads to elevated extracellular 5HT when combined with a systematically administered SSRI (Invernizzi *et al*. 1992, 1996; Hjorth, 1993). However, this mechanism of action does not explain the antidepressant activity of tianeptine because repeated treatment does not enhance 5HT transmission in the rat hippocampus (Pineyro *et al*. 1995*a*, *b*).

Among TCA, clomipramine resembles SSRI (Blier *et al*. 1990) in modifying the function of 5HT containing neurons, while desipramine may increase the release of 5HT by acting on α_2-adrenoceptors at the nerve terminals (Blier *et al*. 1990; Tao & Hjorth, 1992). Therefore, according to de Montigny, TCA and SSRI may achieve the same effect, i.e. increased 5HT neurotransmission, through different mechanisms. It is, however, still under debate whether this effect represents a final common mechanism for antidepressants.

Another mechanism common to most TCA is an increase in dopaminergic transmission. This is unexpected as most AD, with the exception of amineptine, do not affect DA uptake *in vitro* or after acute administration *in vivo* (Ceci *et al*. 1986; Garattini & Mennini, 1989). The explanation includes increased sensitivity of postsynaptic DA receptors (Spyraki & Fibiger, 1981) and decreased sensitivity of pre-synaptic DA receptors (Serra *et al*. 1979). The increased dopaminergic activity in the mesolimbic system (Itoh *et al*. 1990) may indeed be significant because the effect of AD in the despair test is inhibited by DA antagonists (Cervo & Samanin, 1987, 1988). DA_2 antagonists, in particular, but not the DA_1 antagonist SCH 23390, inhibit the action of AD (Borsini *et al*. 1988), indicating that only DA_2 receptor subtypes are involved in the despair test, considered significant as a predictor of antidepressant activity. Sertraline is also effective in this test and its action is antagonized by DA antagonists such as sulpiride (Cervo *et al*. 1991). Other SSRI are not active in the despair test in rats although they are effective in mice (for review, see Borsini, 1995).

The variety of neurochemical effects shown by the various classes of AD is certainly indicative of the fact that antidepressant activity may be achieved by acting on several monoaminergic mechanisms independently from the effect of acute treatment. It is impossible at present to offer any unifying theory, but it is equally difficult to affirm that any particular mechanism set in evidence is the one really responsible for the antidepressant activity. Monoamines certainly seem to be of primary importance, as shown in man. Depressed patients in remission after drug treatment represent rapid relapse of depression after tryptophan depletion (Delgado *et al*. 1990; Barbui & Garattini, 1997; Smith *et al*. 1997). Similarly, depression rating scores increased in desipramine-treated patients in remission when they were given α-methyl p-tyrosine, an inhibitor of tyrosine hydroxylase (Delgado *et al*. 1993). In this case it is difficult to establish whether NA or DA or both were involved.

Besides the mechanisms, it is important to establish whether the various AD have characteristic profiles in inducing the remission of depression. Despite 30 years of clinical studies it is still very difficult to decide which drug should be selected for which depressed patient.

CLINICAL STUDIES

The variety of biochemical effects of AD is not reflected in clinical trials, which are marked by stereotypy (Hotopf *et al*. 1997*a*). A typical trial consists of groups of 50–60 patients with a placebo arm for comparison and a reference drug in another arm, usually imipramine or amitriptyline, for about 6–8 weeks – in striking contrast with the recommended duration of AD treatment which is 4–6 months (Paykel & Priest, 1992; Consensus Committee, 1993). A few instruments, which evaluate a narrow range of clinical parameters, are used to demonstrate antidepressant activity.

Studies use as an endpoint the average difference in the scores from various scales,

rather than the difference between the proportions of non-responders, which would be an obvious main endpoint for the action of an antidepressant. In addition, there is no real agreement on the definition of 'responders to treatment': some studies adopt the cut-off score technique, and others the method of a 50% reduction from the baseline Hamilton Depression Rating Scale (Angst *et al.* 1993). Including only patients who complete treatment in the endpoint analysis does not account for drop-outs, which can amount to a sizable proportion of those recruited.

Study protocols often do not provide justification for the sample size, or even specify their statistical power. Given that the baseline proportion of non-responders ranges between 20 and 30%, it can be reasonably argued that undersized clinical trials (providing very low statistical power for showing any difference between treatments), over very short periods, and excluding non-compliant subjects from the analysis (whatever their reason for non-compliance) would make it implausibly optimistic to expect the absolute difference between active treatments to exceed 20%. In practice, this suggests searching for equivalence, rather than differences, in drug efficacy. The sample size needed to show a difference of 5% between treatments, assuming a baseline rate of 20% of non-responders for the most effective agent, is between 1250 (alpha 0·05 and beta 0·20) and 2380 (alpha 0·01 and beta 0·10) subjects per arm. Clearly these numbers have little in common with most trials.

Studies comparing TCA and SSRI

Song *et al.* (1993) summarized the clinical trials comparing TCA and SSRI that showed very similar results, albeit with remarkably large confidence intervals even on average scores, indicating the very low power of each trial in detecting any 'real' difference between the drugs. These authors also found no substantial differences in the side effects of TCA and SSRI, at least judging from the number of drop-outs.

These data were re-analysed by Montgomery and colleagues (Montgomery *et al.* 1994; Montgomery & Kasper, 1995), who argued that Song *et al.* had grouped atypical antidepressant drugs (for instance trazodone) in the TCA class; they are not widely prescribed and supposedly have fewer side effects than the classical TCA. This new analysis showed a significant difference in drop-outs for side effects, but not for inefficacy, between SSRI and TCA, favouring the SSRI. Since Montgomery *et al.* (1994) did not analyse total drop-out rates, Anderson & Tomenson (1995), to fill this gap, published a meta-analysis of 62 randomized controlled trials comprising 6029 patients with major unipolar depression. Obviously, drop-outs can be due either to side effects or to inefficacy, or both, and their exclusion from the analysis in either case constitutes a serious bias since these are crucial aspects in any overall evaluation of the agents being compared – and particularly since the difference in toxicity between SSRI and TCA is one of the points repeatedly stressed. Anderson & Tomenson reached the conclusion that differences between the two AD were, at most, small. The total drop-outs were 30·8% for SSRI and 34·4% for TCA (Anderson & Tomenson, 1995).

These results must be viewed critically considering that the meta-analysis pools drop-out rates that differed widely between trials (from nil to 80% for individual drugs). Furthermore, the duration of treatment (6–8 weeks) is shorter than the recommended 4–6 months, when drop-out rates may be higher (Fontaine, 1991; Claghorn & Feighner, 1993) and there is about 8% of drop-outs (one-quarter of the total) for each class of drugs that is not specified by Anderson & Tomenson (1995). The differences between TCA and SSRI drop-out rates become less important in trials with more than 70 patients per group. Despite these limitations Anderson & Tomenson conclude that the difference in drop-outs 'is of uncertain importance clinically and when cost-effectiveness is considered'.

Hotopf *et al.* (1997*b*) argued that TCA are heterogeneous with regard to their side effect profile and amitriptyline and imipramine, considered as the reference TCA, have the least favourable risk–benefit profile. Therefore, Hotopf compared the discontinuation rates of SSRI and old tricyclics (imipramine and amitriptyline), newer tricyclics (dothiepin, nortriptyline, desipramine, clomipramine and doxepin) and heterocyclic antidepressants (bupropion, mianserin, trazodone, maprotiline, amineptine and nomifensine). This meta-analysis showed a

slightly lower discontinuation rate of the SSRI than for old tricyclics; however when SSRI were compared with newer tricyclics and heterocyclic AD no significant differences were found in discontinuation rates (Hotopf *et al.* 1997*b*). These data suggest that the advantage of SSRI over TCA in terms of drop-outs might be due to the use of old tricyclics as reference compounds in most controlled trials. This information must be interpreted critically, because the small number of studies comparing SSRI and newer TCA and heterocyclic AD might have lowered the statistical power for detecting any real difference between the treatments. However, the habit of using amitriptyline as reference compound should be discouraged, as it does not represent the 'gold standard' among TCA in terms of side-effects.

Severely depressed patients

On the topic of the severity of depression there is still concern that SSRI may be less effective than TCA in patients with endogenous depression (melancholia) (Potter *et al.* 1991; Anderson & Tomenson, 1994; Meagher & Murray, 1997). Direct comparisons between clomipramine, a TCA with some effects on 5HT uptake, and two newer SSRI, citalopram (Danish University Antidepressant Group, 1986) and paroxetine (Danish University Antidepressant Group, 1990), show that the rate of complete responders was higher for clomipramine (34–65%) than for the two SSRI (22–28%). Paroxetine, in particular, was less effective than clomipramine in depressed inpatients (Anderson & Tomenson, 1994). Data from 19 randomized trials with fluoxetine showed that 10·4% discontinued the treatment for lack of efficacy in comparison with 8·5% receiving TCA; the difference is not statistically significant, but is close to 20% (Pande & Sayler, 1993). Perry (1996) analysed the efficacy of TCA compared with SSRI in major depression with melancholic features by reviewing the Hamilton depression rating scores of controlled trials. TCA were consistently more effective than SSRI, thus supporting the suggestion 'to treat melancholic patients *first* with a course of TCA' (Perry, 1996).

Joffe *et al.* (1996) calculated the effect size of AD therapy in depressive disorders by reviewing studies that included an active drug as well as placebo as reference. The analysis confirmed that 69% of the patients on medication (TCA or SSRI) did better than the average person in the placebo condition; interestingly, however, on adjusting the analysis for a set of predictor variables, TCA tended to have a larger effect size than SSRI (0·511 *v.* 0·464, not significant). Kennedy & Bagby (1996) commented on these data in an editorial stressing the need to demonstrate the SSRI are at least as effective as TCA. Therefore, the question is not which SSRI may be superior to TCA, but whether SSRI are as effective as TCA (Moller & Volz, 1996). This issue probably will be addressed narrowing RCT inclusion criteria to enrol a more severely depressed population, instead of moderately ill patients.

Special groups of patients

The elderly are a special group of depressed patients. TCA are certainly effective (Georgotas *et al.* 1987; Fedoroff & Robinson, 1989; Salzman *et al.* 1993) but the same cannot be said for SSRI because most published trials do not include patients over 65 years. In fact for fluoxetine (Feighner & Cohn, 1985; Altamura *et al.* 1989), sertraline (Cohn *et al.* 1990) and paroxetine (Guillibert *et al.* 1989; Dunner *et al.* 1992) the asserted equivalence in the elderly is obtained using relatively small numbers of patients, suboptimal doses of TCA and without placebo, with the risk that in these trials both classes of drugs may be ineffective for different reasons.

The low quality of controlled trials in this population was recently illustrated by two systematic overviews that made a qualitative analysis of the available literature (Anstey & Brodaty, 1995; Menting *et al.* 1996). They concluded that most questions on the place of AD in the elderly are unanswered because of methodological shortcomings that limit the general applicability of the results.

The complex problem of treating cardiac patients with TCA has been discussed by Glassman *et al.* (1993), who analysed the various facets of the risk–benefit ratio for SSRI. TCA have been considered unsuitable for patients at risk of cardiac diseases because most of them have 'pro-arrhythmic' as well as 'anti-arrhythmic' activity, and may cause orthostatic hypotension and ECG abnormalities (for review see: Halper & Mann, 1988; Glassman *et al.*

1993). However, very few studies have investigated the actual side effects in depressed cardiac patients. It appears that TCA do not reduce ventricular function, they do not exacerbate conduction defects even in patients with ECG abnormalities, and the major problem is orthostatic hypotension.

Not all TCA have the same degree of cardiotoxicity; clomipramine, a non-selective serotonin uptake inhibitor, seems less toxic than other TCA, particularly at high doses (Cassidy & Henry, 1987; McTavish & Benfield, 1990). Fluoxetine and other SSRI are considered to be free of such cardiovascular effects even after overdose (Fish, 1985; Cooper, 1988; Mitchell, 1994). However, the blockade of 5HT uptake, by increasing the level of free 5HT, might affect vasospasm in coronary arteries (Lemberger *et al.* 1985). Fluoxetine and other SSRI have not been specifically studied in patients with cardiac diseases and therefore caution is recommended with regard to their use in this population (Harris & Benfield, 1995).

It is frequently claimed that an advantage of having several drugs available for the treatment of the same disease is the possibility of different options for non-responders. Except for anedoctal reports, there are no controlled trials to indicate that SSRI may be effective in depressed patients resistant to TCA (Nierenberg & McColl, 1996).

Several papers have analysed the relation between treatment with AD and suicide. Henry *et al.* (1995) reviewed the fatal toxicities in 1987–92 in England, Scotland, and Wales, finding that 81·6% (1310/1606) of deaths from AD were due to two drugs: amitriptyline and dothiepin. They also observed that the overall rate of deaths was 34·14 per million prescriptions of TCA, 13·48 for MAO inhibitors, 6·19 for atypical drugs and 2·02 for SSRI. However, Jick *et al.* (1995), in an open cohort study on 172 598 people who had at least one prescription for an AD during the study period, found that the risk of suicide was similar for the various AD, which included both TCA and SSRI. This study confirms a previous meta-analysis (Beasley *et al.* 1991) showing that TCA, fluoxetine or placebo were no different in terms of suicides. Similar findings were obtained by Letizia *et al.* (1996), who conducted a meta-analysis to assess the risk of suicide during treatment with fluvoxamine, TCA and placebo. No differences between fluvoxamine and TCA were observed with regard to the emergence, the worsening and the improvement of suicidal ideation (Letizia *et al.* 1996). Edwards (1995), in an editorial, comments that the AD employed to treat depression may not be very important as people who are determined to kill themselves will choose a means of doing so.

COST AND BENEFIT

A consideration of the array of AD should include an economic evaluation since there are considerable differences in the costs of treatment. Several authors have discussed the relation between TCA and SSRI as regards the cost–benefit ratio. It is rightly argued that the cost of drugs should be assessed against the indirect costs, i.e. time off work, cost of extra treatment, cost of side effects, and other parameters (Beuzen *et al.* 1993; Jonsson & Bebbington, 1994). However, any such analysis has a different meaning depending on the type of health system available in each country. Furthermore, there may be a general bias related to the fact that pharmaco-economic analyses are sponsored by SSRI producing companies (Bentkover & Feighner, 1995; O'Brien *et al.* 1995), while the TCA manufacturers, in view of the low price of their products, have less interest in such studies (Garattini, 1997). Freemantle *et al.* (1994) reported that 'the cost per life year gained through avoiding suicides by the routine first-line use of SSRI is higher than for TCA'.

A recent review of the literature by Hotopf *et al.* (1996) indicates that most authors published indirect economic evaluations, carried out using data from randomized controlled trials (RCT). These studies did not address the issue of the cost-effectiveness of SSRI in comparison to TCA, because of several methodological limitations (extrapolation of data from non-randomized samples of patients, non-random selection of RCT, overestimation of the cost of treatment failure, conflicts of interest) (Hotopf *et al.* 1996): they concluded 'there is no evidence to suggest that SSRI are more cost-effective than TCA'. Woods & Baker (1997) reached a similar conclusion through the analysis of one prospective, four retrospective, and 15 simulation studies comparing newer and older AD. The

prospective pharmacoeconomic study (Simon *et al*. 1996) provided no clear guide to the initial selection of AD therapy for general practice patients.

The monthly cost of therapy in Italy varies widely and in general new drugs – particularly SSRI – are more expensive than the classical TCA. For instance amitriptyline costs Lit. 29500/month and desipramine around Lit. 17700/month, fluoxetine Lit. 85000/month and paroxetine Lit. 103700/month. Since the 'equivalence' of these two drug classes is controversial – in terms of efficacy and side effects – doctors prescribing them should consider the price. Similarly, national health systems must establish which AD are to be reimbursed not only following the criteria of efficacy but also taking into account the cost–benefit ratio. These aspects will undoubtedly receive much more attention in the near future.

CONCLUSION

The problem of treating depression is far from solved despite the large number of drugs available. However, AD have permitted a step forward not only in the treatment of mental disorders but also in the understanding of brain biochemistry and functions. Even so, market needs frequently come before patients' interests. Regulatory authorities must, therefore, review the claims made by some of the old and more recent AD and keep an eye open to the difficulties in evaluating applications for new AD.

We have already discussed the productivity of studies in animals. In view of the nature of the target of AD and the pathway of drug discovery, studies in animals, although necessary, must be regarded with caution. There is, in fact, wide heterogeneity in the action of the various AD that precludes any single theory about the pathogenesis and therapy of depression. It is, therefore, difficult to establish a series of tests to predict AD activity and unconventional new tests need to be developed in the hope of generating AD with an intrinsically different mechanism of action than that produced by modifications of neurotransmission by monoamines, such as dopamine, noradrenaline and serotonin.

As regards the clinical data, there is remarkable variety in the neurochemical differences shown in pre-clinical studies and clinical protocols tend to stereotypy. Although experimentally detected differences are widely exploited in the market promotion of these drugs, attempts at investigating them clinically are still on a far more limited scale. Since so many AD are already available there should be more trials with special groups of populations, as patients with severe depression, non-responders to current treatments, and physically ill depressive patients. In addition, more trials that address the issue of the effectiveness of the various compounds in 'real life' conditions are warranted.

The use of placebo in severely depressed patients is questionable from an ethical point of view. In our view regulatory authorities should require clinical trials to omit placebo and to include adequate controls with one of the established AD drugs, avoiding the use of the reference drugs at sub-optimal doses. The duration of treatments could be initially 6–8 weeks but should then be prolonged to observe the efficacy of the new treatment at 4–6 months, the time usually recommended in clinical practice. The endpoint of the trial should reflect a more critical attitude to the items in the various scales that are changed by treatment. A wider choice of clinical outcome measures should be used so that the diversity that is apparent preclinically may be reflected to some extent in clinical trial outcomes. The number of complete responses may be employed to asses the real efficacy of treatment. Regulators should pay special attention to the so-called equivalence of effects of a new drug in relation to the reference AD. Equivalence must be qualified depending on how powerful the trial is in detecting significant differences. In many cases individual trials do not distinguish a difference of 20%, a real disservice to patients who may be treated with a less effective drug.

Side effects must be detected and carefully evaluated in large-scale trials; they should be actually observed and not only inferred from the lack of changes of specific biochemical or functional parameters. For instance, the advertised superiority of SSRI over TCA for the treatment of elderly depressed patients has not received adequate support from randomized trials. The introduction of new drugs must also be evaluated in relation to their cost: it is hard

to accept the idea that new drugs with equivalent efficacy should cost ten times as much as old drugs. Studies are needed to promote objective comparative evaluation of the cost, benefits and toxic effects of AD. There is a need in this field – as in other areas of therapy – for trials to establish meaningful comparisons, sponsored by the national health services rather than by the producers. On the whole regulatory authorities should become more stringent in the approval of new drugs when such a large number of AD is already available.

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