Antidepressants in the 1990s

EUGENE S. PAYKEL

The development of antidepressants is a continuing process and starting or finishing a review in any particular year risks the creation of arbitrary breaks. However a decade is as reasonable as any other time period to choose for a look to take stock. This editorial will not attempt to be comprehensive, but is a personal view of some issues which have emerged, as seen by a clinician and clinical psychopharmacologist.

It is forty years since the spectacular developments in the late 1950s brought us the two major classes of antidepressants, the reuptake inhibitors and the MAO inhibitors. There are now many such antidepressants licensed and available. In the UK, in 1999 there were 28, ten of them tricyclics, five SSRIs, four other reuptake inhibitors, three older MAO inhibitors, one RIMA and five drugs with other actions. It was in the 1990s that the SSRIs came to particular prominence, although some of them were available a little earlier. They have now been followed by newer drugs with other actions such as venlafaxine, a non-tricyclic serotonin and noradrenaline reuptake inhibitor, reboxetine, a noradrenaline reuptake inhibitor, nefazodone and mirtazepine, with other actions. With the expiry of the patent for fluoxetine it is unlikely that we will see further new SSRIs.

A vigorous debate raged in a number of countries in the earlier part of the decade as to which classes of antidepressant were preferable, the tricyclics or the newer drugs. The tricyclics have the advantage of being much cheaper and there have been very large numbers of trials establishing their efficacy and clinical place. We also know the severity threshold a little below major depression at which their superiority over placebo develops (Paykel *et al.*, 1988; Stewart *et al.*, 1983), although this probably also applies to other antidepressants. On the other hand the tricyclics have lower tolerability and dangers in overdose. Most of the new antidepressants have very specific receptor and other pharmacological effects without as many of the unwanted effects. Prescribing rates for SSRIs and for newer antidepressants have been rising steeply and in most countries the choice for milder depression has moved to the newer drugs. There is still debate as to whether broader spectrum reuptake inhibitors with noradrenergic as well as serotoninergic effects may be more effective in severe depression.

The original impetus for development of SSRIs was the idea that there might be specific serotonin deficient depressions. In fact within depression responsive biochemical subclasses have failed to be confirmed and the advantages of the SSRIs have lain in their better tolerability. What has emerged, somewhat unexpectedly, is the superiority of SSRIs to noradrenaline reuptake inhibitors in certain situations outside depression. This has been seen most clearly in obsessive compulsive disorder. There have been many comparisons of SSRIs versus placebo published in the 1990s, but the conclusive direct comparisons of serotoninergic and noradrenergic drugs in fact took place just before the decade (Thoren *et al.*, 1980; Leonard *et al.* 1988; Goodman *et al.*, 1990). There is suggestive evidence that the same applies for anxiety disorders (Evans *et al.*, 1986; Den Boer & Westenberg 1988; Sasson *et al.*, 1999).

An earlier debate about selectivity concerned the MAO inhibitors. It dates back to early views from St Thomasí Hospital in London, first published by West a& Dally (1959), that these drugs were more effective in atypical depression. This concept has actually meant various things to various people (Paykel *et al.*, 1983). The debate resurfaced in the 1980s with some studies suggesting at least weakly that there was superiority to tricyclics where anxiety was present (Ravaris *et al.*, 1980; Sheehan *et al.*, 1980; Paykel *et al.* 1982; Davidson *et al.*, 1986). A further set of studies from New York indicated superiority of phenelzine over imipramine with a different set of features, a pattern of oversleeping, overeating, leaden fatigue and rejection sensitivity (Liebowitz *et al.*, 1988; Quitkin *et al.* 1988; 1990). Notably even in these studies imipramine was superior to placebo. This

Indirizzo per la corrispondenza: Professor E.S. Paykel, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ (UK).

view of atypical depression has become the standard one in the USA in the 1990s. In fact in most circumstances it is difficult to predict on the basis of clinical features who will respond to a reuptake inhibitor and who to an MAO inhibitor, and the place of the MAO inhibitors is mainly as second line treatments. I have found them useful in bipolar disorder. In the 1990s, the reversible MAO-A selective competitive inhibitor moclobemide became available. It does not appear to affect a different group of patients from those gaining benefit from tricyclics, at least in terms of clinical features (Paykel, 1995).

Whatever the antidepressant, some patients still fail to respond. Only a relatively small proportion of the whole spectrum of depressed patients fails to show any improvement with antidepressants, but such resistant depressives are encountered by all psychiatrists. The augmentation strategy which is now the standard first choice in this situation is addition of lithium, although other combinations such as use with antidepressants of tri-iodothyronine, tryptophan, and combination of non serotoninergic uptake inhibitors with MAO inhibitors, may also have their place.

A combination which has received a good deal of attention in the last few years is that of a serotoninergic antidepressant with the 5HT1A antagonist pindolol. It is based on the hypothesis that early in antidepressant treatment 5HT1A autoreceptors act to diminish the increased neurotransmission and that full therapeutic effects only develop when later subsensitivity of these receptors occurs (Blier *et al.*, 1987). The suggested use of pindolol is really to produce more rapid response rather than more complete response. Five controlled trials of pindolol augmentation of antidepressants have found more rapid response (Maes *et al.*, 1996; Perez *et al.*, 1997; Tome *et al.*, 1997; Zanardi *et al.*, 1997; Bordet *et al.*, 1997) while one has failed to do so (Berman *et al.*, 1997). One study has found augmentation of effects of total sleep deprivation (Smeraldi *et al.*, 1999). The one study of augmentation in resistant depression failed to show benefit (Perez *et al.*, 1999).

A much greater problem than resistant depression is that of partial remission with residual symptoms, which occurs in 20%-30% of depressives (Paykel *et al.*, 1995; Brodaty *et al.*, 1993). These are patients who have not responded fully to antidepressants. Here, two controlled trials indicate that cognitive therapy has a place (Fava *et al.*, 1998; Paykel *et al.*, 1999).

Part of the search for new antidepressants, at least after the first ten years, has been the hope for new drug classes and new pharmacological actions. This has not been easy, since most of the available animal antidepressant screening procedures probably test for the already known pharmacologies. Virtually all the currently marketed antidepressants can be seen as in some way or other to have primary effects which increase neurotransmission by noradrenaline, serotonin, or both, most commonly by inhibition of presynaptic reuptake, inhibition of intraneuronal breakdown by MAO-A, or in a few drugs presynaptic noradrenaline autoreceptor antagonism, or other effects on 5HT receptors. For a small number of drugs marketed in some countries, such as buproprion or tianeptine, effects are less clear-cut and easily explained in this way, but for the most part when drugs with novel pharmacologies have seemed promising, they have in the long run turned out to be disappointing.

The latest and currently promising novel drug is a substance P antagonist, in its first published controlled trial, superior to placebo and comparable to paroxetine (Kramer *et al.*, 1998). It is still too early to tell whether this will represent a new and effective class of antidepressant.

No matter how effective the antidepressants, the efficacy cannot be achieved unless they are used properly. The 1990s have seen considerable investment in guidelines for use and in educational campaigns to improve usage in practice (Paykel & Priest, 1992; American Psychiatric Association, 1993; Paykel *et al.*, 1997). Attitudes of the general public to antidepressants, at least in the UK, partly explain the reluctance to take them and poor compliance often found in acute treatment. In a general population survey a high proportion of subjects viewed antidepressants as addictive and they were considerably more positive regarding the use of counselling than of antidepressants in treatment of depression (Paykel *et al.*, 1998).

The last fifteen years have also been a period of disappointment in one aspect: the longer term outcome of depression is still often far from ideal, characterised by high rates of relapse and recurrence. The finding of this pattern, in spite of the availability of modern treatments emerged conclusively in follow-up studies in the later 1980s (Keller *et al.*, 1984; Kiloh *et al.*, 1988; Lee & Murray, 1988). Antidepressants are markedly superior to placebo in controlled trials of continuation therapy over about six months after remission. Antidepressants and mood stabilisers are also superior but less strikingly so in longer term maintenance therapy (Paykel, 1996). There are some discrepancies between the marked therapeutic benefit found in controlled trials of long term medication and the high relapse and recurrence rates which remain in practice. This does not appear to be due in large measure to failure to administer medication (Ra-

mana *et al.*, 1999). Probably some of the paradox is resolved by considering the samples in maintenance trials, which often comprise patients who have responded to acute treatment with the particular antidepressant being evaluated, and in modern studies, have remained well for six months continuation, and who in addition have been selected by inclusion criteria for recurrent disorders. Such patients, benefiting particularly from medication during acute treatment and continuation are most likely to benefit during maintenance and to show worse outcome when withdrawn to placebo.

Part of the story may also have to do with the speed of withdrawal of medication. For lithium, high rates of early relapse have been found in bipolars in a naturalistic study after drug withdrawal (Suppes *et al.*, 1991). In another naturalistic study relapse rates were lower after slow withdrawal of lithium than after abrupt withdrawal (Faedda *et al.*, 1993). There are withdrawal reactions from very abrupt withdrawal, both of tricyclics and of SSRIs (Rosenbaum *et al.*, 1998). Although conclusive evidence has not so far been presented for antidepressants that relatively rapid although not abrupt withdrawal increases relapse rates compared with slow withdrawal, there is suggestive evidence that this is the case (Kupfer 1991). There is a prudent message for clinical practice which has still not been widely formulated at the end of the 1990s. Continuation and maintenance antidepressants should always be withdrawn slowly over three months or more rather than over a few weeks or less.

REFERENCES

American Psychiatric Association (1993). Practice guidelines for major depressive disorder in adults. *American Journal of Psychiatry* 150, Suppl. 4, 1-26.

Berman R.M., Darnell A.M., Miller H.L., Anand A. & Charney D.S.. (1997). Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double blind, placebo-controlled trial. *American Journal of Psychiatry* 154, 37-43.

Blier P., de Montigny C. & Chaput Y. (1987). Modifications of the serotonin system by antidepressant treatments: implications for the therapeutic response in major depression. *Journal of Clinical Psychopharmacology* 7, Suppl. 6, 245-355.

Bordet R., Thomas P. & Dupuis B. (1997). Effect of pindolol on onset of action of paroxetine in the treatment of major depression: intermediate analysis of a double-blind, placebo-controlled trial. *American Journal of Psychiatry* 155, 1346-1351.

Brodaty H., Harris L., Peters K., Wilhelm K., Hidkie I., Boyce P., Mitchell P., Parker G. & Eyers K. (1993). Prognosis of depression in the elderly: a comparison with younger patients. *British Journal of Psychiatry* 163, 589-596.

Davidson J., Pleton S., Krishnan R.R. & Allf B. (1986). The Newcastle Anxiety Depression Index in relationship to the effects of MAOI and TCA drugs. *Journal of Affective Disorders* 11, 51-61.

Den Boer J.A. & Westenberg H.G.M. (1988). Effect of serotonin and noradrenaline uptake inhibitors in panic disorders: a double-blind comparative study with fluvoxamine and maprotiline. *International Journal of Clinical Psychopharmacology* 3, 59-74.

Evans L., Kenardy J., Schneider P. & Hoey H. (1986). Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. A double-blind comparison of zimeldine, imipramine and placebo. *Acta Psychiatrica Scandinavica* 73, 49-53.

Faedda G.L., Tondon L., Baldessarini R.J., Suppes T. & Tohen M. (1993). Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Archives of General Psychiatry* 50, 448-455.

Fava G.A., Rafanelli C., Grandi S., Canestrari R. & Morphy M.A. (1998). Six year outcome for cognitive behavioural treatment of residual symptoms in major depression. *American Journal of Psychiatry* 155, 1443-1445.

Goodman W.K., Price L.H., Delgado P.L., Palumbo J., Krystal J.H., Nagy L.M., Rasmussen S.A., Heninger G.R. & Charney D.S. (1990). Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder. *Archives of General Psychiatry* 47, 577-585.

Keller M.B., Klerman G.L., Lavori P.W., Coryell W., Endicott J. & Taylor J.. (1984). Long-term outcome of episodes of major depression: clinical and public health significance. *Journal of the American Medical Association* 252, 788-792.

Kiloh L.G., Andrews G.A. & Neilson M. (1988). The long-term outcome of depressive illness. *British Journal of Psychiatry* 153, 752-757.

Kramer M.S., Cutler N., Feighner J., Shrivastava R., Carman J., Sramek J.J., Reines S.A., Liu G., Snavely D., Wyatt-Knowles E., Hale J.J., Mills S.G., MacCoss M., Swain C.J., Harrison T., Hill R.G., Hefti F., Scolnick E.M., Cascieri M.A., Chicchi G.G., Smith D., Carlson E.J., Hargreaves R.J. & Rupniak N.M.J. (1998). Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 281, 1640-1645.

Kupfer D.J. (1991). Long-term treatment of depression. *Journal of Clinical Psychiatry* 52, Suppl. May, 28-34.

Lee A.S. & Murray R.M.. (1988). The long-term outcome of Maudsley depressives. *British Journal of Psychiatry* 153, 741-751.

Leonard H., Swedo S., Rapoport J.L., Coffey M. & Cheslow D. (1988). Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine: a double-blind crossover comparison. *Psychopharmacological Bulletin* 24, 93-95.

Liebowitz W.R., Quitkin F.M., Stewart J.W., McGrath P., Harrison W.M., Markowitz J.A., Rabkin J.G., Tricamo E., Goetz D.M. & Klein D.F. (1988). Antidepressant specificity in atypical depression. *Archives of General Psychiatry* 45, 129-137.

Maes M., Vandoolaeghe E. & Desnyder R. (1996). Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *Journal of Affective Disorders* 41, 201-210.

Paykel E.S. (1995). Clinical efficacy of reversible and selective inhibitors of monamine oxidase A in major depression. *Acta Psychiatrica Scandinavica* 91, Suppl. 386, 22-27.

Paykel E.S. (1996). Tertiary prevention: longer-term drug treatment in depression. In *The Prevention of Mental Illness in Primary Care* (ed. T. Kendrick, A. Tylee and P Freeling), pp. 281-293. Cambridge University Press: Cambridge.

Paykel E.S. & Priest R.G. (1992). Recognition and management of depression in general practice: consensus statement. *British Medical Journal* 305, 1198-1202.

Paykel E.S., Ramana R., Cooper Z., Hayhurst H., Kerr J. & Barocka A. (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* 25, 1171-1180.

Paykel E.S., Rowan P.R., Parker R.R. & Bhat A.V. (1982). Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Archives of General Psychiatry* 39, 1041-1049.

Paykel E.S., Parker R.R., Rowan P.R., Rao B.M. & Taylor C.N. (1983). Nosology of atypical depression. *Psychological Medicine* 13, 131-139.

Paykel E.S., Hollyman J.A., Freeling P. & Sedgwick P. (1988). Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *Journal of Affective Disorders* 14, 83-95.

Paykel E.S., Tylee A., Wright A., Priest R.G., Rix S .& Hart D. (1997). The Defeat Depression Campaign: psychiatry in the public arena. *American Journal of Psychiatry* 154, Suppl. 6, 59-65.

Paykel E.S., Hart D. & Priest R.G.. (1998). Changes in public attitudes to depression during the Defeat Depression Campaign. *British Journal of Psychiatry* 173, 519-522.

Paykel E.S., Scott J., Teasdale J.D., Johnson A.L., Garland A., Moore R., Jenaway A., Cornwall P.L., Hayhurst H., Abbott R. & Pope M. (1999). Prevention of relapse by cognitive therapy in residual depression: a controlled trial. *Archives of General Psychiatry* 56, 829-835.

Perez V., Gilaberte I., Faries D., Alvarez E. & Artigas F. (1997). Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet* 349, 1594-1597.

Perez V., Soler J., Puigdemont D. & Alvarez E. (1999). A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Archives of General Psychiatry* 56, 375-379.

Quitkin F.M., Steward J.W., McGrath P.J., Liebowitz J.R., Harrison W.M., Tricamo E., Klein D.F., Rabkin J.G., Wager S. & Markowitz J. (1988). Phenelzine versus imipramine in the treatment of probably atypical depression: defining syndrome boundaries of selective MAOI responders. *American Journal of Psychiatry* 145, 306-311.

Quitkin F.M., McGrath P.J., Stewart J.W., Harrison W., Tricamo E., Wager S.G., Ocepek-Welikson K. & Nunes E. (1990). Atypical depression, panic attacks and response to imipramine and phenelzine. *Archives of General Psychiatry* 47, 935-941.

Ramana R., Paykel E.S., Surtees P.G., Melzer D. & Mehta M. (1999). Medication received by patients with depression following the acute episode: adequacy and relation to outcome. *British Journal of Psychiatry* 174, 128-134.

Ravaris C.L., Robinson D.S., Ives J.O., Nies A. & Bartlett D. (1980). Phenelzine and amitriptyline in the treatment of depression. *Archives of General Psychiatry* 37, 1076-1080.

Rosenbaum J.F., Fava M., Hong S.L., Ascroft R.C. & Krebs W. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological Psychiatry* 44, 77-87.

Sasson Y. Iancu I., Fux M., Taub M., Dannon P.N. & Zohar J. (1999). A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. *European Neuropsychopharmacology* 9, 191-196.

Sheehan D., Ballenger J. & Jacobsen G. (1980). Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Archives of General Psychiatry* 36, 51-59.

Smeraldi E., Benedetti F., Barbini B., Campori E. & Colombo C. (1999). Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression: a placebo controlled trial. *Neuropsychopharmacology* 20, 380-385.

Stewart J.W., Quitkin F., Liebowitz M.R., McGrath P.J., Harrison W., & Klein D.F. (1983). Efficacy of desipramine in depressed outpatients: response according to Research Diagnostic Criteria and severity of illness. *Archives of General Psychiatry* 40, 202-207.

Suppes T., Baldessarini R.J., Faedda G.L. & Tohen M. (1991). Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Archives of General Psychiatry* 48, 1082-1088.

Thoren P., Asberg M., Cronholm B., Jornested T.L. & Träskman L. (1980). Clomipramine treatment of obsessive-compulsive disorder 1: a controled clinical trial. *Archives of General Psychiatry* 37, 1281-1285.

Tome M.B., Isaac M.T. & Holland C. (1997). Paroxetine and pindolol: a randomised trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *International Clinical Psychopharmacology* 12, 81-89.

West E.D. & Dally P.J. (1959). Effects of iproniazid in depressive syndromes. *British Medical Journal* 1, 1491-1499.

Zanardi R., Artigas F., Franchini L., Sforzini L., Gasperini M., Semraldi E. & Perez J. (1997). How long should pindolol be associated with paroxetine to improve the antidepressant response? *Journal of Clinical Psychopharmacology* 17, 446-450.