improving understanding of relative benefits of interventions. Whilst the results of meta-analyses may be readily accessible, they are limited by the quality of the original RCTs. Systematic reviews involve the identification and qualitative assessment of all trials. We argue that systematic reviews may provide information of greater value, both to researchers and clinicians, since they illustrate the limitations of trials and ultimately of meta-analysis. 105 RCTs and four meta-analyses have failed to provide a clear answer to the question of whether selective serotonin reuptake inhibitors (SSRIs) or tricyclic/heterocyclic antidepressants should be used as first line treatment for depression in primary care settings. We will present a systematic review which examines the quality of trials and meta-analysis presenting some quantitative findings. The key findings of the systematic review are that the majority of trials are small, fail to conduct intention to treat analyses, are based in secondary care where only a minority of patients are treated, use observer rated assessments of depressive symptoms which are open to observer bias, and fail to give economic evaluations. We performed a meta-analysis using drop outs from treatment and found that overall the SSRIs had a modest advantage over tricyclics and heterocyclics (Risk Ratio 0.90; (95% CI: 0.86–0.97)). We formulated the *a priori* hypothesis that this effect would be strongest when older tricyclics were used as the comparison group, due to their more prominent side effects. We found that the SSRIs maintained their advantage when compared with the older tricyclics, amitriptyline and imipramine (RR 0.88; 95% CI: 0.82–0.95). When compared with newer tricyclics or heterocyclics no significant advantage for the SSRIs could be found (RR = 0.92; (95% CI: 0.82–1.04) for new tricyclics, and RR 1.02; (95% CI: 0.83–1.25) for heterocyclics). We suggest that the poor quality of many trials and these still equivocal results, based on drop out not clinical recovery, indicate a need for a large RCT based in primary care, and using a newer tricyclic as the comparison drug.

S51. Novel antidepressants

Chairmen: H Freeman, B Leonard

CHANGES IN 5-HT RECEPTOR SENSITIVITY DURING TREATMENT WITH SSRIs: IMPLICATIONS FOR MODE OF ACTION

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The acute pharmacological effect of selective serotonin re-uptake inhibitors (SSRIs) is essentially confined to the blockade of serotonin (5-HT) re-uptake. SSRIs are effective antidepressants and block 5-HT re-uptake a few hours after a single administration. Their antidepressant effect, however, takes several days to become apparent.

Recent animal experimental investigations have suggested that adaptive changes in 5-HT receptors may play an important role in mediating the antidepressant effects of SSRIs and, perhaps, account for the delay in onset of therapeutic effect. One popular theory suggests that acute administration of SSRIs does not increase overall 5-HT neurotransmission because activation of somatodendritic 5-HT_{1A} autoreceptors attenuates the firing of 5-HT neurones. With continued treatment, however, there is an evolving desensitisation of 5-HT_{1A} autoreceptors which permits a sustained increase in 5-HT neurotransmission. In addition, continued treatment with SSRIs may desensitise the $5\text{-HT}_{1B/1D}$ nerve terminal autoreceptor, again facilitating 5-HT release.

Neuroendocrine studies in our laboratory with the selective 5-HT_{1A} agonist, gepirone, and the 5-HT_{1D} agonist, sumatriptan, suggest that SSRIs do indeed desensitise 5-HT_{1A} receptors, but 5-HT_{1D} receptors were unaffected. These findings are of interest in view of reports that co-administration of SSRIs with the 5-HT_{1A} receptor antagonist, pindolol, can speed the onset of antidepressant effect. Drugs that produce acute increases in 5-HT neurotransmission may therefore have an earlier onset of action than conventional antidepressant compounds.

TOLERABILITY AND SAFETY OF NOVEL ANTIDEPRESSANTS

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As a group, the novel antidepressants (such as selective serotonin reuptake inhibitors, venlafaxine, nefazodone and mirtazapine) compared to older tricyclics show substantially lower incidences of adverse events in general, and improved safety due to a reduction of anticholinergic side effects. This finding is consistent with the fact that novel antidepressants are developed to be more selective in their mechanism of action. In the case of the SSRIs, the pharmacological action is exerted almost exclusively via the serotonergic (5-HT) system. However, their non-specific actions at receptor level, through stimulation of all 5-HT receptors, give rise to a variety of typical side effects, namely gastrointestinal side effects such as nausea and vomiting, headache, insomnia, restlessness and symptoms of sexual dysfunction. Venlafaxine inhibits reuptake of both noradrenaline (NA) and 5-HT, but because of a lack of receptor-specific actions its side effect profile still shows similarities with both the TCAs and SSRIs. Nefazodone, in addition to inhibiting 5-HT reuptake, specifically blocks 5-HT_2 receptors. This profile results in substantial reduction of 5-HT_2-mediated side effects, namely nervousness, insomnia, diarrhoea and sexual dysfunction. Mirtazapine combines enhancement of both NA and 5-HT neurotransmission by blocking α_2 adrenoceptors with specific blockade of 5-HT_2 and 5-HT_3 receptors. As a result, the incidences of anti-adrenergic and serotonergic side effects are comparable to placebo. Transient initial somnolence can be related to its antihistaminergic properties. In conclusion, the selective receptor actions of new antidepressants result in a substantial improvement in their overall tolerability and safety. The data suggest that the receptor-specific antidepressants which will become available throughout Europe during the years to come show a significantly better tolerability profile which may improve compliance and decrease the burden of pharmacological therapy without influencing efficacy.

NEW TRENDS IN THE PHARMACOLOGICAL TREATMENT OF DEPRESSION

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The need to develop new antidepressants has been motivated by the frequency and potential severity of the adverse effects of the tricyclic and monoamine oxidase inhibitor antidepressants. This search for new classes of antidepressants has led to the development of selective inhibitors of noradrenaline or serotonin (5-hydroxytryptamine; 5-HT) reuptake, reversible inhibitors of monoamine oxidase, and noradrenergic and specific serotonergic antidepressants. More recently, novel antidepressants such as mirtazapine, which modulate both noradrenergic and different populations of 5-HT receptors, have been developed. However, while such novel antidepressants have different pharmacological profiles, there is no evidence that their therapeutic

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efficacy is superior to that of the tricyclic antidepressants. This raises the question of whether there is a common mechanism of antidepressant effects that may be activated via different neurochemical processes. Some of the possible mechanisms whereby chronic administration of antidepressants may elicit adaptive changes in serotonergic, noradrenergic and other neurotransmitter systems are discussed against the background to the biochemical basis of depression. Finally, the need to improve the efficacy of antidepressants, possibly by utilising mechanisms other than those involving direct modulation of monoamine neurotransmitters (e.g. by changes in prostaglandins, cytokines and neuropeptides such as corticotrophin-releasing factor) will be considered.

MIRTAZAPINE

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There are three established mechanisms that produce clinical defined antidepressant activity; blockade of monoamine reuptake, prevention of monoamine breakdown by monoamine oxidase inhibition, and blockade of monoamine receptors. The prototype of this third class of antidepressant is mianserin, whose mode of action was thought to be due to blockade of presynaptic inhibitory α_2-adrenoceptors and postsynaptic 5-HT_2 and 5-HT_3 receptors. Mirtazapine represents the next generation of this class of drug, having the same actions at these three classes of receptor but being free of the other unwanted actions of mianserin, namely the sedative ones that came from blockade of histamine and α_1-adrenoceptors. Thus, mirtazapine increases the availability of noradrenaline in the brain by disinhibiting tonic activity at presynaptic autoreceptors. In addition, mirtazapine blocks similar inhibitory α_2-adrenoceptors on 5-HT terminals, it also increases the release of 5-HT. However, as it also inhibits 5-HT_2 and 5-HT_3 receptors, mirtazapine should be free from some of the side effects that emerge from a more general increase in brain 5-HT, such as produced by the SSRIs.

Clinical studies comparing mirtazapine with placebo and comparator antidepressants confirm the predictions from the preclinical studies. It is effective against placebo and equivalent to comparator drugs; it has good tolerability in general and shows a low propensity to provoke anxiety or agitation, or the sleep disruption that can be a feature of treatment with SSRIs. It thus appears, that mirtazapine is a pharmacologically novel antidepressant that represents a useful addition to the formulary.

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S52. Mood disturbances, psychoses and epilepsy

Chairmen: F Monaco, EH Reynolds

THERAPEUTIC ASPECTS OF DEPRESSION IN EPILEPSY: THE IMPACT OF DRUG INTERACTIONS

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The impact of drug interactions on the rational treatment of depression in epilepsy is quite relevant, both from the pharmacokinetic and the pharmacodynamic point of view. It must also be remembered that some anticonvulsants (i.e., carbamazepine, valproic acid and, more recently, lamotrigine) are also used in the therapy of depression in association with other antidepressants (AD).

In general, antiepileptic drugs (AED) cause a reduction of AD plasma levels (chlomipramine, imipramine, nortriptiline, amitriptyline, mianserine, nomiphensine), with the consequent risk of an insufficient therapeutic effect.

On the other hand, classic tricyclic AD usually cause an increase of AED plasma levels.

Some of these potential interactive effects are also shared by the SSRI-AD, which, though in different ways for each different drug (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) may cause an increase of concomitant tricyclic AD and AED, through the inhibition of the isoenzyme P50 IID6.

An area of particular interest is the one concerning the phenomena of potentiation and/or antagonism at the drug's site of action in the CNS. Coadministration of AD and AED, infact, may exert severe neurotoxic effects in some cases, with possible impairment of cognitive functions. Therapeutic drug monitoring of plasma AED and AD levels, whenever available and indicated, allows the clinician to evaluate the kinetic modifications in the course of such combined therapies thus tailoring the posology to individual needs.

THERAPEUTIC ASPECTS OF DEPRESSION AND EPILEPSY: NEW VS. OLD ANTIEPILEPTIC DRUGS

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The symptom depression is frequently associated with epilepsy and, therefore, the problem rises on how this symptom can be prevented and/or adequately controlled. Among traditional antiepileptic drugs, phenobarbital and primidone are known to induce depression, while valproic acid and, especially, carbamazepine have proved to exert beneficial effects on mood disturbances. In recent years, a number of new antiepileptic drugs have entered the marketing and are now available for clinical use. Some of these new drugs, especially vigabatrin and lamotrigine, have been seen to influence mood in some way.

Whether or not the observed effects of all these antiepileptic drugs are secondary to their effect on epileptic seizures or are independent from this is not fully elucidated at the present.

The main pharmacokinetic and pharmacodynamic properties of some conventional and new drugs together with their effect on mood will be reviewed briefly with the aim of facilitating a more rational use in clinical practice.

DEPRESSION IN PEOPLE WITH EPILEPSY

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Depression is a common complication in people with epilepsy (PWE). It has been shown that the depression is associated with both psychosocial and neuroepilepsy variables. Thus, in some instances, psychosocial stressors such as increased life events, poor adjustment to seizures and financial stresses may contribute to depression in PWE. Other aetiological factors include a family history of depression and/or suicide. Several investigations have found that the depression appears to be associated with complex partial seizures (CPS) and temporal lobe epilepsy (TLE), when compared to generalised epilepsy (GE). Moreover left sided lesions may be particularly implicated. Depression may also be associated with the duration of epilepsy and a past history of depression. Finally, antiepileptic drugs (AEDs) have a significant effect on mood, with phenobarbitone being

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