S59-6
OPTIMISING COMPLIANCE WITH TREATMENT

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It is well established that antidepressants, antipsychotics and mood stabilisers prevent relapse if taken long-term. Patients however, will only comply with medication if they accept that something is wrong with themselves, that it needs correcting, that drugs correct it and that the risk:benefit ratio to them is acceptable. Common reasons for discontinuing psychotropics include side effects (even though these can often be managed), fear of addiction, lack of knowledge that drugs prevent relapse and (usually uninformed) pressure from friends and relatives.

A positive attitude towards drugs is generally essential for compliance or concordance, particularly in the long-term. Current compliance techniques tend to revolve around provision of information using the traditional sender-message-receiver communication model. A number of studies have shown the advantages of structured education of patients and the subsequent positive effect on attitude and hence compliance and relapse. Individual or group sessions covering dependence, chronic and acute illness, how drugs work etc. improve attitude to drugs, particularly if follow-up or reinforcing support material and resources are available. Pharmaceutical care of patients e.g. by structured education, will minimise negative attitudes towards drugs and reduce relapse.

S60. Biological and clinical aspects of treatment-resistant depression

Chairs: J Mendlewicz (B), P Bech (DK)

S60-1
DEFINITION CRITERIA FOR TREATMENT RESISTANT DEPRESSION

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Outcome studies have demonstrated that approximately one third of patients treated for major depression do not respond satisfactorily to antidepressant pharmacotherapy. Long term observations reveal that a considerable number of patients have a poor prognosis, with as many as 20 percent remaining unwell two years after the onset of the illness. These outcome data are usually used to estimate the frequency of Treatment Resistant Depression (TRD). The key parameters that characterize and define TRD include the basic criteria used to specify the diagnosis, the response to treatment, previous treatment trials, the adequacy of treatment and compliance to treatment. Diagnostic aspects include the need to reach an accurate diagnosis; the various forms of treatment relating to other subtypes of depressive disorders; comorbidity with other psychiatric or personality disorders and chronicity. The assessment of treatment response raises the problems of how to evaluate remission and the minimum length of remission required. Previous failed treatment trials remain a subject of controversy and refer to the number and type of adequate antidepressant treatment trials required by the patient before the question of resistance can be considered. Finally, treatment adequacy has to be considered in terms of dosage, duration and compliance. A lack of consensus on these points restricts comparison between clinical trials and limits interpretation of the efficacy of treatment in the management of treatment resistant patients. We have re-examined the available data in TRD to indicate the limitations of the existing definitions and we propose conceptual and operational criteria for collaborative research projects. It appears that a number of variables commonly associated with treatment resistance, relate mainly to misdiagnosis and inadequate treatment and are independent of the characteristics of patients. The proposed criteria are intended for use in therapeutic trials in TRD, both to evaluate the efficacy of treatment and to examine the conceptual aspects of the subject. In major depression, the operational definition we propose for TRD is a failure to respond to two adequate consecutive trials of treatment with different classes of antidepressants. The rationale for this definition is discussed in the context of alternative definitions.

S60-2
CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF RESISTANT DEPRESSION

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During the last decades, it has been a constant that about 1/3 of depressed do not respond to antidepressants: this is true across diagnostic subgroups and pharmacological mechanisms of action. 20% of patients treated are still ill 2 years after onset (Paykel 1994) and 10% resist to multiple interventions (Nieremberg & Amsterdam 1990). In the NCA, a small proportion of patients represents most of the morbidity and cost.

Therefore, even if resistant depression in no way can be considered a diagnosis per see, it is a practical and theoretical problem of great importance. No agreement on the definition exists since this is a multifactorial problem. Prevalence is obviously influenced by the definition of treatment response (full, partial), on the definition of what an "adequate" treatment or an "aggressive" treatment is (dose + duration), and on the number of failed trials to acknowledge resistance.

The factors usually involved in resistance will be discussed. These are:

- Misdiagnosis and/or diagnostic subtypes. A special attention should be given to comorbidity with other axis I disorders, with axis II disorders, with alcohol and drug addiction and with physical problems such as thyroid dysfunction, neurological disorders or drug treatment of physical condition. However, most studies exclude comorbidity.
- Inadequate treatment is a major cause and probably explains up to 2/3 of resistant patients. The switch from one class (e.g.: SSRIs) to another (e.g.: TCAs) may improve response although some data suggest that moving from an SSRI to another may also be effective.
- Evolution is also a major factor: a) the duration between onset of symptoms and onset of treatment is related to response, b) the persistence after treatment of residual symptomatology may predict long term and poor outcome and therefore resistance.

Discussions about resistance within specialists are only the top of the iceberg when evaluating the situation in primary care. It is proposed that pharmacological resistance should be separated from patient resistant and management resistance.

S60-3
NEUROBIOLOGY OF RESISTANT DEPRESSION

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Patients for whom the diagnosis of depression was established and who did not respond to adequate treatment are defined as suffering

https://doi.org/10.1016/S0924-9338(99)80269-7 Published online by Cambridge University Press

from resistant depression (RD). As between 20–30% of depressed patients have RD, the presence of depression subtypes with distinct pathophysiology is suggested. The neurobiological approach to RD is aimed at identifying and characterizing these different subtypes of RD. Different underlying mechanisms which may play a role in RD include: the development of tolerance ("escape"), a "kindling" type of phenomenon, or no response to begin with. Different types of underlying pathophysiological mechanisms have been proposed for RD, including: higher incidence of HPA axis hyperactivity, lower availability of l-tryptophan to the brain, frontal or parietal perfusion defects, genetic factors, subtle abnormalities in the thyroid system, a combination of 5HT/HPA axis and brain lesion, or a combination of 5HT, NA and HPA abnormalities. In order to gain better knowledge of these different options, studies with RD patients, that provide a careful evaluation of the HPA axis and of serotonergic and noradrenergic responsivity, as well as evaluation of the thyroid system, are warranted. Tryptophan depletion and NE depletion have proven to be an effective tool in the study of depression and might be of particular interest in RD. Brain imaging, pre- and post-treatment, and a dichotomous comparison of changes in brain activity in patients who responded to treatment for RD might be of value. However, these have not yet been studied systematically. A combination of brain imaging with pharmacological challenge, or depletion with either 5HT or NE, might be of particular value, as these combine the "activation" of depression with a "snap shot" of brain activity. Patients with RD suffer greatly and need to be treated. Underlying various psychobiological abnormalities might assist us in tailoring a treatment specifically to the patient.

S60-4

PHARMACODYNAMICS AND PHARMACOKINETICS AS A POSSIBLE CAUSALITY IN RESISTANT DEPRESSION

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Treatment resistant depression (TRD) may involve various degrees of disequilibrium between pharmacodynamic and pharmacokinetic variables. The key neurotransmitters implicated in the actiology of depression are serotonin (5-HT), norepinephrine (NE) and dopamine (DA).

The ability of depletion strategies, which decrease 5-HT activity (administration of para-chlorophenylalanine (PCPA) or a low tryptophan diet), creates treatment resistance to the effect of antidepressants. This evidence strongly supports the importance of 5-HT for TRD.

There is limited evidence for a possible causal relationship between dysfunctional central NA and DA neurotransmission and TRD. However, it has been shown that: the addition of reserpine to tricyclic antidepressants (TCA) might augment the antidepressant effects in TRD; yohimbine, an alpha-2-blocker, may potentiate TCA therapy.

In the last years we have investigated the interactions between all three monoamine systems implicated in antidepressant action by studying the role of intracellular messengers which may represent a common target in the action of different antidepressants. In particular data on the effects of serotonin reuptake inhibitors (SSRI), SNRI and TCAs on the modifications of specific phosphoproteins and on the activity of protein kinases located at pre- and postsynaptic level will be presented.

Moreover, large individual differences in metabolism might represent a rationale for refractory depression.

In conclusion this presentation will deal with pharmacodynamic and pharmacokinetic factors with the aim to establish a possible casual relationship in TRD.

S60-5

GENERAL THERAPEUTIC STRATEGIES IN TRD: LIMITATIONS AND PROSPECTS

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Current strategies for treatment of resistant depression have been based on the results from a small number of controlled studies and to a larger extent on the possibly overoptimistic reporting of open case studies. The treatment of resistant depression needs to address the most common causes of non response, which are inappropriate dosage of antidepressants and poor compliance, before initiating more sophisticated approaches. Initially the antidepressant should be used in full or appropriate doses with adequate checks on individual metabolism or on compliance using drug plasma level monitoring where appropriate.

The results of investigations of the provocation of depression using pharmacological probes suggest that some depressions have a selective response to SSRIs while others are noradrenergic. These findings suggest a rational basis for (a) switching between different classes of an antidepressant in the case of nonresponse, or (b) augmenting an SSRI with a NARI or vice versa. A similar case can be made to suggest that double action antidpressants, eg venlafaxine, milnacipran, clomipramine or mirtazapine, might be tried in resistant depression although only venlafaxine has been studied in this population. Of the other augmentation strategies lithium is the best established and the use of T3 or of pindolol the least.

Some depressions appear to be truly refractory. Recurrent brief depression is the most common category with a prevalence as high as major depression. Recurrent brief depression does not appear to respond to SSRIs, RIMAs, or TCAs in placebo-controlled studies and more treatment studies are urgently needed.

S60-6

AUGMENTATION STRATEGIES IN TREATMENT RESISTANT DEPRESSION: PRECLINICAL AND CLINICAL ASPECTS

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Several augmentation strategies have been devised over the last two decades. This presentation will focus on two of them: lithium and pindolol additions in treatment-resistant depression.

Lithium, even when administered at low doses, increases rapidly the function of (5-HT) neurons. Using single cell recording, we have shown that a short-term (2 or 3 days) lithium treatment enhances the efficacy of the stimulation of the ascending 5-HT pathway in suppressing the firing activity of dorsal hippocampus pyramidal neurons and that this phenomenon was attributable to a presynaptic effect of lithium. However, there is some evidence from other groups that a sub-set of 5-HT_{1A} receptors might be sensitized by short-term lithium.

The efficacy of lithium addition in treatment-resistant depression has been thoroughly documented. The most striking feature is perhaps that lithium has been found to potentiate all types of antidepressant treatments tested thus far (including sleep deprivation). The onset of action varies greatly: some patients improved within 24–72 hrs, while a fair number will show a significant improvement only after two weeks.

https://doi.org/10.1016/S0924-9338(99)80269-7 Published online by Cambridge University Press