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

Giorgio Racagni. *Center of Neuropharmacology, Inst. of Pharmacological Sciences, University of Milan; I.R.C.C.S. Center San Giovanni di Dio-Fatebenefratelli, Brescia, Italy*

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

S.A. Montgomery. *Imperial College School of Medicine, London, UK*

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

Claude de Montigny*, Pierre Blier. *Neurobiological Psychiatry Unit, McGill University, Montréal, Québec H3A 1A1, Canada*

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 $5\text{-HT}_{1A}$ 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.

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(–)Pindolol is a /5-$HT_{1A}$ antagonist. With the group of F. Artigas, we have shown that pindolol in the rat can block the somatodendritic 5-$HT_{1A}$ autoreceptor in the dorsal raphe without affecting the responsiveness of postsynaptic 5-$HT_{1A}$ receptors in the dorsal hippocampus.

Many clinical trials have shown a highly significant acceleration of the antidepressant response by combining (±) pindolol (2.5 mg TID) to an SSRI. Preliminary data suggests that pindolol addition may be efficacious in some treatment-resistant depression. Importantly, in contrast with lithium, pindolol addition to non-serotonergic antidepressant drug is without beneficial effect.

# SEC62. Child psychiatry

*Chairs*: J Dias Cordeiro (P), JA Costa e Silva (WHO, CH)

## SEC62-1

ADOLESCENT LIAISON PSYCHIATRY: ETHICAL AND LEGAL ISSUES

António Barbosa. *Department of Liaison Psychiatry, Clínica Psiquiátrica Universitária, Hospital Santa Maria, Lisbon, Portugal*

The field of liaison psychiatry in recent years has expanded significantly into different specialized fields. Liaison psychiatry is being welcome in a context of contemporary medical practice with the even-increasing pace of technology, organizational constraints, all in the context of limited economic resources, because it provides an effective and affective balance to the professional practices.

It is not surprising that liaison psychiatrists are therefore confronted with a myriad of clinical-legal-ethical issues. All true psychiatrists are not expected to be bioethicists, their role in clarifying ambiguities and resolving conflicts between patients-families often lead them directly into legal-ethical issues.

We describe two clinical cases in which the liaison psychiatrist was confronted with problems such as: confidentiality, right to refuse treatment, informed consent, substitute decision making, intra-familiar and intra-team conflicts, developmental issues in adolescence. All this are areas in which frequent clinical-legal dilemmas arise and the liaison psychiatrist must be comfortable with his role of creating a productive disturbance-raising questions and feelings of other professionals. To do so he must actively aware of legal aspects and must have a thorough understanding of ethical reasoning for effective practice of psychiatry in medical settings.

Thus, the competency to engage in moral reasoning and to make critical ethical decisions should be a core component in the training and technical repertoire of liaison psychiatrists.

## SEC62-2

PREVENTION AND EARLY TREATMENT OF SUBSTANCE ABUSE: ETHICAL ASPECTS

D. Bailly. *Child and Adolescent Psychiatry Department, University Hospital of Lille, France*

Alcohol and drug abuse problems take a remarkable toll worldwide. In terms of prevention and early treatment, there is no population more important than adolescents. Epidemiological studies clearly show that substance abuse has its onset during adolescence. However, in terms of prevalence and developmental task perspective, substance use appears as a normative phenomenon. Experimentation with psychoactive substances is reported as an indication of psychological health in adolescents. Studies show that youngsters who have experimented with psychoactive substances are psychologically healthier than other frequent users on abstainers. Given the present cultural norms, substance use is the rule rather than the exception, and the majority of adolescents who engage in substance use do not escalate to abuse. This suggests that the etiology of abuse is distinct from the etiology of use. By this way, many studies show that substance use is a product of social, situational, and environmental determinants, while a substance abuse is the consequence of biological, physiological and psychiatric determinants. If intervention decisions are often focussed on substance use, these considerations question the validity of this approach.

## SEC62-3

No abstract received

## SEC62-4

EARLY DEVELOPMENTAL PREDICTORS OF ADOLESCENT PSYCHOPATHOLOGY

A. Ram*, L. Kikinzon, F. Ladame, A. Braconnier, A. Weizman, S. Tyano. *The Gehah Psychiatric Hospital, The Rabin Medical Center, Tel-Aviv University Medical School, 49100 Petah-Tiqva, Israel*

The present study was designed to detect early predictors of specific psychopathology in adolescents. The study was conducted in adolescent outpatient clinics in three mental health centers (Paris, Geneve and Tel-Aviv). The population included 742 adolescent outpatients. We used 94 items questionnaire which included information concerning demographic, developmental, functional and psychopathological parameters of the adolescents.

The patients were diagnosed according to the DSM-IIIR criteria and divided to 5 major diagnostic categories: psychotic disorders, mood disorders, anxiety disorders, disruptive disorders, adjustment disorders. Controls were subjects who were referred to diagnostic procedure and no axis I positive diagnoses were detected.

A significant correlation was found between developmental pathology during early childhood and disruptive diagnostic category of adolescence (conduct disorder, ADHD, oppositional-defiant disorder, substance abuse and impulse control disorders). It is concluded that early developmental deviations are predictors of the development of disruptive disorders at adolescence.

## SEC62-5

A COMPARATIVE MULTINATIONAL EPIDEMIOLOGICAL STUDY OF ADOLESCENT OUTPATIENT CLINICS

L. Kikinzon*, A. Ram, F. Ladame, A. Braconnier, A. Weizman, S. Tyano. *The Gehah Psychiatric Hospital, The Rabin Medical Center, Tel-Aviv University Medical School, 49100 Petah-Tiqva, Israel*

A multinational epidemiological comparative study of adolescent outpatient clinics was performed in three mental health centers (Geneve, Paris and Tel-Aviv). The purpose of the study was to characterize demographic features in adolescents referred to psychiatric consultation and/or treatment in the different centers. The population included 759 adolescent outpatients (age 12–20 years). We used 94 items questionnaire which included demographic, developmental, functional and psychopathological data of the adolescents.

Significant differences were found between the three centers in parameters of age at the time of referral, socio-economical status