The World Journal of Biological Psychiatry

VOLUME 6

Supplement 2 , 2005

World Federation of Societies of Biological Psychiatry
30th Anniversary Celebration
1 November 2004
Buenos Aires, Argentina

LECTURES

The World Journal of Biological Psychiatry

Volume 6 - Supplement 2 - 2005 Pages 1–64

The Official Journal of the World Federation of Societies of Biological Psychiatry

The World Journal of Biological Psychiatry

Volume 6, Supplement 2, 2005

Contents

Introduction

Lectures

WFSBP Celebrating 30 YEARS of Excellence in Biological Psychiatry

1 November 2004 - Sheraton Hotel, Buenos Aires, Argentina

From left to right:
Professor van Praag, Professor Fink, Professor Ayuso, Professor Hojaij, Professor Gattaz, Doctor Krebs, Professor Altamura, Professor Helmchen

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 3–4

INTRODUCTION

WFSBP Celebrating 30 YEARS of Excellence in Biological Psychiatry

Beyond Boundaries – Across Borders

The history of the World Federation of Societies of Biological Psychiatry remains to be written. However, there are already many things to be said on that leading organisation.

Everything starts in 1974 when Edmond Fisher, Hungarian immigrant in Buenos Aires, Argentina, decides to organize the first international congress dedicated to Biological Psychiatry. Edmond Fisher's vision and leadership encouraged many psychiatrists from different parts of the world to create an international organization for the promotion and development of biological psychiatry.

Along the years, the flag of the World Federation of Societies of Biological Psychiatry crossed innumerable countries and was reduplicated in several of them. Nowadays, psychiatrists from more than 105 countries are taken up in the Federation's database, and societies are established in 60 countries. Initially based in some American and European areas, after societies of biological psychiatry were founded in all Latin American nations, the number of national societies has progressively kept increasing, mainly due to the enthusiastic expansion of biological psychiatry in Asia and Central Europe.

From an amateurish management relying on the good will and personal dedication of its Executive members, the Federation progressed to a modern and well-structured organization, with several departments responsible for a variety of tasks, from the daily contacts with members to the complex organization of congresses. In 1997 the Federation decided to make its administration a professional matter: from the simple but important minutes taken during the meetings to a more precise description of each Executive Committee member's tasks, to the implementation of a central secretariat able to manage and control all activities directed by the Executive Committee, to the legal registration as a not-profitable organization in Switzerland and the establishment of a specific bank account in Switzerland, to the regular audits by authorized accountants, to the full management of its congresses, etc.

With so many psychiatrists and countries joining the Federation, the creation of a number of Sub-Committees and Task Forces dedicated to specific topics was a need that led to numerous productions and publications. Innovatively, all members of the Sub-Committees and Task-Forces were chosen upon suggestions coming from the National Societies. This represented an additional step towards the fundamental principle that the Federation does exist based on its membership.

One of the most significant demonstrations of the Federation's new aptitudes was shown in the creation of *The World Journal of Biological Psychiatry* in 1998. In Sao Paulo, the Executive Committee agreed on starting to launch what would become, in a very short period of time, one of the most important publications in psychiatry.

A few years ago the Constitution was modified in order to give a fair political balance to all National Societies. In the Federation arena all National Societies democratically share political power.

To protect the Federation and the benefits it provides to registered members, a WFSBP Members Identification Card was recently created, allowing access to benefits, such as: reduced registration fee at congresses, restricted areas of the WFSBP web-site, participation in Committees and Task-Forces, a free copy of *The World Journal of Biological Psychiatry*, as well the right to vote, and be voted for, at the Council Meeting and General Assembly.

For being based upon National Societies representing countries all over the world and, consequently, having to incorporate psychiatrists from different cultures in all activities, the Federation aims at accepting and promoting diversity: in other words, the Federation praises diversity, understanding that progress arises from the confrontation of differences. WFSBP constitutes a unique international arena of biological psychiatry which represents and integrates the richness of so many cultures. On top of this, as the Federation also recognizes differences in terms of development, it endeavours to promote education in its highest principle, a principle that all doctors learn at school: the one who knows more has the moral obligation to transfer knowledge to the one who knows less. This goes to show that one of the major tasks that the Federation

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030009

has in its hands is related to the educational activities at congresses and special programmes.

A few months ago, a small logo was published on the Federation website: a flying dove over the sentence "Justice and Peace. We all are responsible". Although the Federation is not a political body, and accepts neither any political activity nor the use of its name and image for any political purpose, the fact that we are all being threatened by loss of freedom again, and that we have to face so many calamities affecting different ethnic groups and threatening the human species, a call for moral consciousness is the least the Organization should do, hoping that the force of awareness and consequent vigilance will bring justice and peace to the worldwide community.

Nowadays, the Federation is an international, modern, active and well-recognized organization, thanks to the dedication and efforts of so many members during this short 30-year history.

If the present is gratifying, the Federation has an immense future. The astonishing progresses of research and treatments in the biological field presents psychiatry as one of the already most advanced and yet promising medical specialties. The Federation arena is the universal ground where knowledge and results are presented and shared.

This supplement is the proceedings of a one-day scientific session in the city of Buenos Aires (Argentina) on 1 November 2004 to celebrate the 30th Anniversary of WFSBP. The Federation expressly invited Carlo Altamura (Italy), Jose Luis Ayuso-Gutierrez (Spain), Max Fink (United States), Wagner Gattaz (Brazil), Hanfried Helmchen (Germany), Marie-Odile Krebs (France), and Herman van Praag (The Netherlands). They form the restricted group of colleagues that moderated and promoted a stimulating discussion with the attendees. It is a privilege for *The World Journal of Biological Psychiatry* to have the opportunity to publish such original and interesting material. I take this opportunity to once more express my warmest gratitude to those colleagues who understood the importance of that meeting and dedicated their precious time to firstly come to Buenos Aires and secondly to reproduce their lectures in written form.

Carlos Roberto Hojaij
Past President, WFSBP

Correspondence:
The Melbourne Institute of Biological Psychiatry
511 Whitehorse Road
Surey Hills 3127
Melbourne
Australia
E-mail: crhojaij@bigpond.com

ACKNOWLEDGEMENT

The current WFSBP President, Professor Siegfried Kasper, would like to pay tribute to all WFSBP Past Presidents and all colleagues who have worked under their leadership for their precious contributions to the advancement of the Federation throughout its 30 years of existence:

1974–1975: Edmund Fisher (Argentina)
1975–1978: Juan Obiols (Spain)
1978–1981: Carlo Perri (Sweden)
1981–1985: Charles Shagass (USA)
1985–1991: Tetsuo Fukuda (Japan)
1991–1997: Jorge Ciprian-Ollivier (Argentina)
1997–2001: Hans-Jürgen Möller (Germany)
2001–2005: Carlos Roberto Hojaij (Australia)

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 5–22

LECTURE

Can stress cause depression?*

HERMAN M. VAN PRAAG

Department of Psychiatry and Neuropsychology, Academic Hospital Maastricht, and the Brain and Behavior Research Institute, Maastricht University, Maastricht, The Netherlands

Abstract
The central issue raised in this paper is: can stress *cause* depression? Phrased more precisely: can stress *cause* brain disturbances thought to underlie (certain forms of) depression or particular components of the depressive syndrome. Focussing on 5-HT and the stress hormones, this question was answered in the affirmative, based on the following two considerations: (1) changes in the 5-HT and stress hormone systems produced by sustained stress, mimic to a substantial extent the disturbances in these systems that may be observed in depression; (2) substantial evidence indicates that the 5-HT and stress hormone disturbances in depression are of pathophysiological significance and not merely a consequence of the depressed state or a product of stress generated by the depressed state. Furthermore, the question was raised whether a depression type could be identified particularly stress-inducible. This question, too, was answered in the affirmative. The depression type in question was named anxiety/aggression-driven depression and characterized on three levels: psychopathologically, biologically and psychologically. Preferential treatment of this depression type was discussed. In studying stress-inducible depression biological depression research should shift focus from depression per se to the neurobiological sequelae of stress. Treatment of stress-inducible depressions and particularly its prevention should be geared towards reduction of stress and stress sensitiveness, utilising both biological and psychological means.

Key words: *Stress, serotonin, cortisol, CRH, anxiety/aggression-driven depression*

Abbreviations: *ACTH, adrenocorticotrophic hormone, AVP, arginine vasopressin, CNS, Central nervous system, CSF, cerebrospinal fluid, CRH, corticotropin releasing hormone, DHEA, dehydroepiandrosterone, DHEA-S, dehydroepiandrosterone sulphate, GR, glucocorticoid receptors, 5-HIAA, 5-hydroxy indole acetic acid, 5-HT, 5-hydroxytryptamine (serotonin), 5-HTP, 5-hydroxytryptophan, HPA, hypothalamic–pituitary–adrenal axis, MR, mineralocorticoid receptors, PVN, paraventricular nucleus, PET, positron emission tomography, PTSD, posttraumatic stress disorder, SSRI, selective serotonin reuptake inhibitor*

Introduction

Can stress cause depression? This is a rather fundamental question. If so, biological depression *research* should shift focus from depression per se to the stress syndromes, while *treatment* of depression, in that case, would be a treatment in the last resort, only to be instituted if treatment of the stress syndrome has been omitted or has failed.

Can stress cause depression? This question is generally answered affirmatively, based on two considerations (Van Praag et al. 2004). First, depression is often preceded by stressors, or stressful situations. Second, preceding depression stressors are much more frequent than in the general population. These data, however, constitute at best suggestive evidence, because it is often so hard to decide whether the stressor is cause or consequence of the depression or of the distressed state that so often precedes depression. Conclusive evidence that stress indeed may *cause* depression requires demonstration that this condition can derail cerebral circuits supposedly underlying depression or certain depressive features.

This then is the question I will discuss. Can stress alter the functioning of particular brain systems in a depressogenic direction. I will be conventional, in

Correspondence: Herman M. van Praag, Department of Psychiatry and Neuropsychology, Academic Hospital Maastricht, and the Brain and Behavior Research Institute, Maastricht University, P.O. box 616, 6200 MD Maastricht, The Netherlands. Tel: +31 55 5760795. Fax: +31 55 5775612. E-mail: h.m.van.praag@vanpraag.com

*A paper of similar tenor was published in *Prog Neuro-Psychopharmacol Biol Psychiatry* 28:891–907, 2004.

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030018

that I focus on two systems that have been studied from the dawn of biological depression research on, i.e. monoamines and in particular 5-hydroxytryptamine (5-HT, serotonin), and the corticotrophin-releasing hormone (CRH)/cortisol systems. Neurosteroids, neurotrophins, the glutamate system – more recent foci of interest – will be left aside, because, as yet, not enough is known about their causal significance in depression.

Serotonin (5-HT) and depression

5-HT metabolism

Several observations point to a deficit in 5-HT metabolism in depression, or, rather, in a subgroup of depression. In the late 1960s, several authors reported lowering of cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA) in some depressives (Van Praag 1969; Van Praag et al. 1970; Van Praag and Korf 1971; Asberg et al. 1976). The major degradation product of 5-HT, 5-HIAA, is found in the CSF as well as in the brain itself. 5-HIAA in lumbar CSF originates partly in the brain, partly in the spinal cord. Both animal (Mignot et al. 1985) and human (post mortem) studies (Stanley et al. 1985) have revealed a close correlation between brain and CSF 5-HIAA. Furthermore, the 5-HIAA concentration in the brain is to a large extent a function of 5-HT metabolism. Therefore CSF 5-HIAA can be considered as an indicator (albeit it a crude indicator) of 5-HT metabolism in (certain parts of) the brain. Low CSF 5-HIAA, thus, suggests lowering of 5-HT metabolism in (certain parts?) of the central nervous system (CNS).

Subsequently this tentative conclusion was supported by several lines of evidence. First, the abundant data that the various classes of antidepressants as well as electroconvulsive treatment, improve the efficiency of 5-HT-ergic transmission, particularly of 5-HT_{1A} receptor-mediated transmission. This happens either by sensitization of postsynaptic 5-HT receptors or by desensitization of presynaptic 5-HT receptors that normally reduce the release of 5-HT in the synaptic cleft or inhibit the firing rate of the 5-HT nerve cell (Blier and de Montigny 1994).

A second group of data is derived from the so-called tryptophan-depletion strategy (Young et al. 1985). Tryptophan is an essential aminoacid and the precursor of 5-HT. A shortage of tryptophan will lead to a deficiency of 5-HT. Such a shortage can be generated by ingesting a mixture of amino acids, devoided of tryptophan and rich in competing amino acids, i.e. amino acids competing with tryptophan for the same transport mechanism from the blood stream into the CNS. This leads to rapid decrease of tryptophan in the blood stream (Delgado et al. 1989), lowering of 5-HIAA in the CSF (Williams et al. 1999) and, in animals, to substantial lowering of brain 5-HT (Moja et al. 1989).

Applied to normal volunteers this procedure leads to the occurrence of mood lowering (Young et al. 1985), in particular in those individuals with a family history of depression (but without having gone through depressive episodes themselves) (Benkelfat et al. 1994; Klaassen et al. 1999a,b) (Figure 1). Patients in remission from an episode of major depression, who responded to tryptophan depletion with mood lowering, showed an increased relapse risk in the next 12 months (Moreno et al. 2000). Depletion of 5-HT but not of NA induces a relapse in depressed patients in remission after treatment with 5-HT specific antidepressants (Delgado and Moreno 2000). Conversely, treatment with the 5-HT precursor, 5-hydroxytryptophan (5-HTP), in combination with a peripheral decarboxylase inhibitor, led to amelioration of depression, in particular in patients with low CSF 5-HIAA (Van Praag and De Haan 1980a,b).

Furthermore (some) depressed patients exhibit reduced tryptophan availability in plasma (Maes et al. 1990), reduced increase in plasma 5-hydroxytryptophan (5-HTP) after an oral load with L-tryptophan (Deakin et al. 1990) and decreased uptake of 5-HTP across the blood–brain barrier (Agren et al. 1991; Agren and Reibring 1994). These data, too, suggest a defect in the synthesis of 5-HT.

Direct measurement of 5-HT synthetic capacity is presently possible by positron emission tomography (PET), measuring the trapping of the tracer [α-^{11}C] methyl-L-tryptophan (α-MTrp) into the synthesis of 5-HT. α-MTrp is a synthetic analog of L-tryptophan. Its methyl group prevents incorporation of the tracer in protein metabolism (Diksic et al. 1990), but does

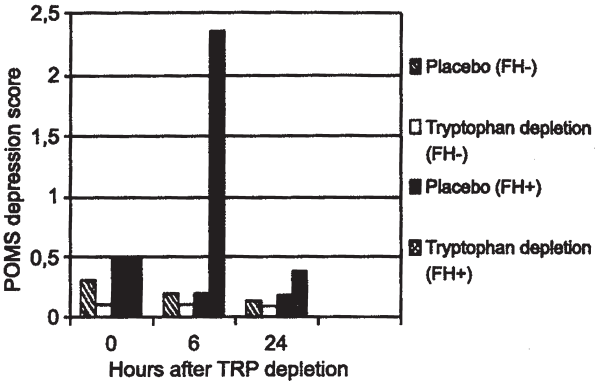


Figure 1. Effect of tryptophan depletion on mood, in normal individuals with or without positive family history for depression. Tryptophan depletion generates pronounced mood lowering for a brief period (Klaassen et al. 1999). FH = family history.

not interfere with its incorporation in the synthesis of 5-HT. The rate of trapping of α-MTrp is considered to be an index of 5-HT synthetic capacity (Chugani and Muzik 2000). Low 5-HT synthesis capacity has been found in impulsive subjects with borderline personality disorder (Leyton et al. 2001), a disorder often complicated by depressive symptoms, as well as in depression in particular in those patients with high impulsivity (Benkelfat et al. 2002).

Three further observations important in this context should be mentioned.

First, lowering of CSF 5-HIAA in a subgroup of depression, appears to be a trait-related phenomenon: it does not disappear after remission of the depression (Van Praag 1977, 1992a; Träskman-Bendz et al. 1984). Marginal 5-HT production possibly represents a vulnerability factor, increasing the risk of depression in times of mounting stress (Van Praag 1988). This hypothesis is supported by the finding that treatment with l-5-HTP, a 5-HT precursor the brain readily transforms into 5-HT, has therapeutic and prophylactic efficacy in depression, in particular in those with signs of deficient 5-HT metabolism (Van Praag and De Haan 1980a,b).

Second, lowered CSF 5-HIAA in depression was shown to correlate positively with increased anxiety (Van Praag 1988) and with manifestations of increased aggression, both inward (Asberg et al. 1976) and outward (Linnoila et al. 1983; Coccaro 1992; Virkkunen et al. 1994) directed aggression (Table I, Figures 2 and 3).

Third, the association of low CSF 5-HIAA and increased anxiety and aggression is demonstrable across diagnoses. Apparently it is independent of the nosological context in which the increase in anxiety and aggression occurs (Van Praag et al. 1987; Van Praag 1997a). These biological disturbances are what we have called functionally specific, i.e. linked to disturbances in psychic functions, rather than nosologically specific, i.e. linked to a particular disease entity (Van Praag 2000).

Table I. Low 5-HIAA depressives compared to normal 5-HIAA depressives present (Van Praag 1988).

Finding	P
More suicide attempts	<0.01
Greater number of contacts with police	<0.05
Increased arguments with	
Relatives	<0.05
Spouse	<0.01
Colleagues	<0.05
Friends	<0.05
More hostility at interview	<0.05
Impaired employment history (arguments)	<0.05

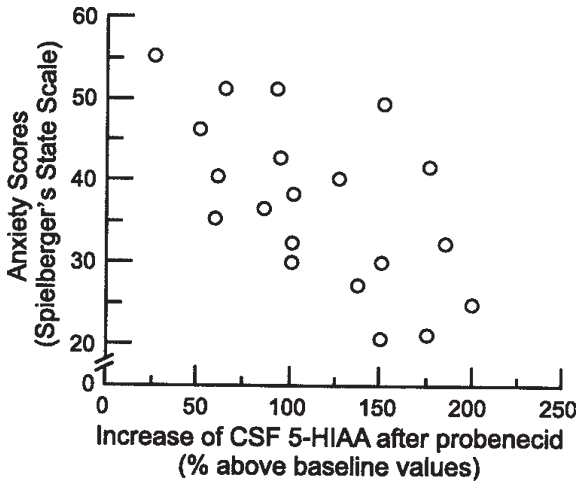


Figure 2. Post-probenecid CSF 5-HIAA concentration in patients with major depression, melancholic type. This variable correlates negatively with trait anxiety scores (Van Praag 1988).

5-HT receptor disturbances

Besides metabolic disturbances, receptor disturbances have been found in depression; again, not in depression as such but in a subgroup of depression.

The 5-HT system operates via a great number, at least 15, probably function-specific receptors. They are subdivided into seven subtypes, named 5-HT_1, 5-HT_2...5-HT_7 receptors. The 5-HT_1 receptor family is subdivided into four subgroups 5-HT_{1A} up to 5-HT_{1D}, the 5-HT_2 family counts three subtypes: 5-HT_{2A} up to 5-HT_{2C} receptors.

5-HT_{1A} receptors are located both pre- and postsynaptically. The presynaptic 5-HT_{1A} receptor is located on the cell bodies and involved in negative feedback regulation of the 5-HT neuron. Its activation leads to reduction in firing rate. The 5-HT_{1D} receptor (analogous with the 5-HT_{1B} receptor in

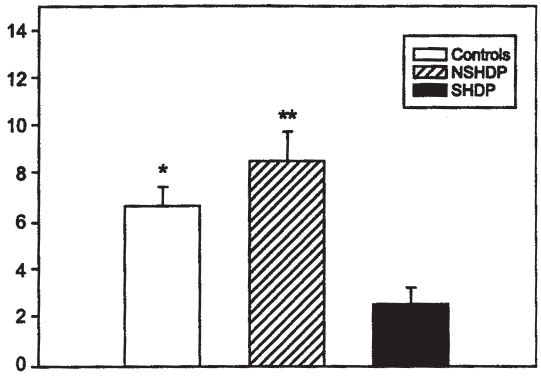


Figure 3. Peak prolactin response to d-fenfluramine in healthy controls and a group of patients with major depression with or without a history of suicide attempts. The prolactin response was blunted in the suicidal depressed group (SHDP) relative to the non-suicidal depressed group (NSHDP) and the control group (Corrêa et al. 2000).

rodents) is also found pre- and postsynaptically. The presynaptic receptor is located on the presynaptic membrane and functions likewise as a '5-HT brake': its activation leads to diminution of 5-HT release.

In humans, 5-HT receptors have been predominantly studied with challenge tests. To the extent that selective ligands have become available, PET and SPECT studies recently have assumed an ever more important role. In most challenge tests *indirect* 5-HT agonists have been used, such as the 5-HT precursors, tryptophan and 5-HTP, as well as fenfluramine, a 5-HT releaser and inhibitor of its reuptake (Newman et al. 1998). The secretion of prolactin and ACTH by the pituitary gland and of cortisol by the adrenal cortex have been mostly used as serotonergically mediated variables.

Most of those studies reported blunting of the hormonal responses to indirect 5-HT agonists in a subgroup of depression (Ansseau 1997; Newman et al. 1998), indicating downregulation of 5-HT receptors. The prolactin responses to fenfluramine and to the selective serotonin reuptake inhibitor (SSRI) citalopram remain blunted in recovered patients (Florey et al. 1998). The cortisol response to citalopram on the other hand does normalize (Bhagwagar et al. 2002). These findings suggest that some aspects of impaired 5-HT-ergic transmission are trait-markers, just as low CSF 5-HIAA is.

Indirect 5-HT agonists act presynaptically and hence increase 5-HT availability throughout the entire 5-HT system. They do not provide information as to which of the some 15 different subtypes of 5-HT receptors are actually downregulated. To this end one needs selective and direct agonists (or antagonists) of each of the receptor subtypes. Only few of those are available for use in humans.

Highly selective, full, pre- or postsynaptic *5-HT_{1A} agonists or antagonists* have not yet been studied in humans. Data are available regarding a few azapirone derivatives, i.e. ipsaperone, giperone and buspirone. Those compounds are partial agonists of the 5-HT_{1A} receptor and not very selective ones: their main metabolite 1-phenyl-piperazine, for instance, is also a α_2-adrenergic antagonist. Blocking of this presynaptically located adrenergic receptor, present on both 5-HT-ergic and NA-ergic neurons, could lead to increased 5-HT and NA release and thus contribute to antidepressant effects. In addition, these drugs activate the D_2 receptor, particularly buspirone.

Several studies reported blunted hormonal responses after an ipsaperone challenge in (a subgroup of) depression, as well as attenuation of buspirone-induced hypothermia, suggesting abnormal functioning of the 5-HT_{1A} receptor (Lesch et al. 1990; Cowen and Wood 1991). As mentioned, this receptor is located both post- and presynaptically. The presynaptic 5-HT_{1A} receptors are located on the cell bodies and dendritic branches of 5-HT-ergic neurons. They play an important role in feedback inhibition of the 5-HT-ergic neuron. Stimulation of a 5-HT-ergic nerve cell leads to release of 5-HT not only in the synaptic cleft but also in the region of the soma (cell body). The somatodendritic 5-HT_{1A} receptor is thus activated, which leads to inhibition of the firing rate of the 5-HT-ergic neuron. Blunted hormonal responses to ipsaperone could thus mean: hyporesponsivity of the postsynaptic 5-HT_{1A} receptor or hyperresponsivity of its presynaptic equivalent. Since, normally, after administration of ipsaperone, the release of hormones like prolactin and cortisol increases, activation of the postsynaptic receptor evidently supersedes that of the presynaptic receptor and hence blunting of the ipsaperone response can be regarded as an indication of downregulation of the postsynaptic 5-HT_{1A} receptor.

PET studies provided direct evidence for 5-HT_{1A} receptor pathology in depression. A widespread reduction in 5-HT_{1A} receptor binding was reported in patients with major depression, both presynaptically in the raphe nuclei – and postsynaptically, i.e. in several cortical regions (Drevets et al. 1999; Sargent et al. 2000) (Figure 4). After remission an increase

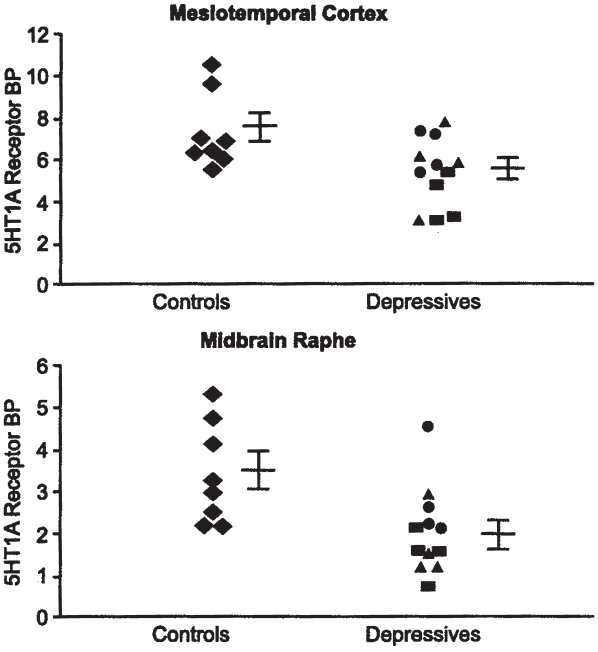


Figure 4. Scatter histograms of the 5-HT_{1a} receptor binding potential values for depressed patients and a control group. Within the depressed sample, circles indicate unipolar depressives with only major depressive disorder relatives, triangles indicate unipolar depressives with bipolar depressive (BD) relatives, and squares designate BD depressives with BD relatives. Mean and standard error bars appear to the right of each data set (Drevets et al. 1999).

failed to occur. 5-HT_{1A} receptor disturbances in depression, thus, possess trait-character, possibly representing risk factors for depression. This phenomenon, too, is not categorically – (i.e. depression-) specific. Decreased 5-HT_{1A} density has also been demonstrated in panic disorder (Charney, 2004).

The hypothesis that 5-HT_{1A} receptor pathology is involved in the pathophysiology of (certain types of) depression or certain components of the depressive syndrome is supported by animal data.

In animal models of depression (particularly the forced swimming test and the learned helplessness test), highly selective 5-HT_{1A} receptor agonists possess antidepressant properties (Mayorga et al. 2001). In addition they exert antiaggressive and anxiolytic effects (Borsini et al. 1999). Mice lacking the 5-HT_{1A} receptor show increased anxiety (Parks et al. 1998). Several lines of evidence indicate that these are postsynaptic effects. This was most elegantly demonstrated by Gross et al. (2002). They developed a method to knock out and restore the 5-HT_{1A} receptor locally, and demonstrated that anxiety-like behaviour was only produced if 5-HT_{1A} receptors in the forebrain were deleted, not if their presynaptic counterpart in the raphe nuclei were knocked out.

Some evidence suggests that the postsynaptic *5-HT_{1D} receptor* may be hyporesponsive in depression. Challenge tests with zolmitripan, a 5-HT_{1D} receptor agonist that penetrates the brain fairly well, leads to increased release of growth hormone, supposedly via activation of postsynaptic 5-HT_{1D} receptors. In depression, particularly melancholic depression, the growth hormone response to zolmitripan was found to be blunted (Whale et al. 2001). Activation of the postsynaptic receptor has strong aggression-reducing effects; knocking-out the 5-HT_{1B} receptor in mice leads to enhancement of aggressive behaviour (Sandou et al. 1994). Some animal data suggest that the 5-HT_{1B} receptor is involved in antidepressant drug action in animal models of depression (Redrobe et al. 1996). Human data indicating antidepressant activity of postsynaptic 5-HT_{1D} receptors agonists however, are lacking.

The status of the *5-HT_2 receptor* in depression is uncertain. This receptor type has been studied with challenge tests, using the relative selective 5-HT_{2C} agonist, *m*-chlorophenylpiperazine (mCPP). It is an anxiogenic substance and may provoke panic attacks in patients with panic disorder; while, in addition, the hormonal responses to mCPP are above average, indicating supersensitivity of this receptor. Patients suffering from generalized anxiety disorder or panic disorder, also showed increased hostility rating after mCPP administration. Normal subjects did not (Germine et al. 1992). In depression, the sensitivity of the 5-HT_{2C} receptor has been found to be increased (Riedel et al. 2002).

Peripherally, in blood platelets, upregulation of 5-$HT_{2(A)}$ receptors has been frequently observed in depressed patients (Pandey et al. 1990), particularly in suicidal depressed patients (Hrdina et al. 1993) and in assaultive personality disordered individuals (Coccaro et al. 1997). However negative reports have also been published (Cowen et al. 1987).

Brain imaging studies, on the other hand, showed mixed results. In a single photon emission computer tomography (SPECT) study D'Haenen et al. (1992) found increased 5-$HT_{2(A)}$ receptor binding. PET studies revealed no change (Meyer et al. 1999) or a decrease (Yatham et al. 2000; Audenaert et al. 2001). The decrease, however, could have been caused by previous antidepressant treatment (Yatham et al. 1999). Moreover, different receptor ligands were used.

In favour of a role for 5-HT_2 receptor overactivity in the pathophysiology of depression speaks the observation that 5-HT_2 receptor antagonists and inverse agonists have been shown to possess antidepressant potential in animal models (Bromidge et al. 2000; Yamada and Sugimoto 2001).

Summary

A decrease of 5-HT metabolism has been ascertained in the brain of a subgroup of depression: this phenomenon is trait-related and associated with heightened anxiety and increased aggression, both inwardly and outwardly directed aggression across diagnoses.

In addition, 5-HT receptor disturbances may be observed in this type of patients. The data are most firm for the 5-HT_{1A} receptor that was found to be downregulated in a trait-related fashion. Based on animal data, one can assume this phenomenon to be associated with increased anxiety and aggression.

The data on other 5-HT receptors that have been studied in humans are tentative. Some evidence suggests the 5-HT_{1D} receptor to be hyposensitive, and the 5-HT_{2C} receptor to be hypersensitive. The former phenomenon can be expected to increase the aggression level, the latter phenomenon the anxiety level.

It is well known that in some depressives, increased anxiety and aggression are prominent features.

Stress hormones and depression

Excess cortisol

Since the introduction of the antidepressants, monoamines have been a major focus of biological depression research. A second line of intense in-

vestigation relates to the hypothalamic–pituitary–adrenal (HPA) axis. It received its major impetus from the work of Sachar et al. (1973), showing around the clock elevation of plasma cortisol concentrations in depression and an altered circadian pattern of cortisol secretion. The frequency, duration and magnitude of secretory busts are increased. The usual dip between 20.00 and 02.00 h disappears; instead, cortisol hypersecretion continues. Sachar and his group were not the first to report on hypercortisolemia in depression (Board et al. 1956), but it was the first detailed 24-h study.

Depressed patients with high resting plasma cortisol, still show a substantial cortisol response to physiological or psychological stressors. Failure to limit the stress-induced cortisol response will, thus, result in greater overall exposure to cortisol. Assuming excess cortisol to be related to behavioural changes, a vicious circle will therefore be initiated (Young et al. 2000). Two types of corticosteroid receptors have been described in the brain: mineralocorticoid receptors (MRs, or type I receptors) and glucocorticoid receptors (GRs, or type II receptors) (De Kloet and Reul 1987; De Kloet 1991). MRs bind to mineralocorticoids such as aldosterone but to glucocorticoids as well, and even with higher affinity. Cortisol binds to both MRs and GRs, but it has 10 times higher affinity for MRs. Under normal conditions MRs are already largely occupied, in contrast to the GRs. MRs, therefore, control basal HPA activity. When cortisol levels rise, such as under conditions of stress, GRs become more and more occupied. This provides the signal for reduction of HPA axis activity. MRs being activated at low cortisol concentrations and GRs activated at higher cortisol concentration enable the brain to respond appropriately to a range of cortisol concentrations (Joëls and De Kloet 1994; Holsboer 2000).

Other signs of HPA axis overdrive

Many additional data indicate that the HPA system may be hyperactive in depression. Pertinent are the following observations (Arborelius et al. 1999; Holsboer 2000).

- Increased level of circulating ACTH.
- Increased urinary cortisol excretion.
- Increased levels of CRH in CSF (Figure 5) and an increased number of CRH secreting neurons and CRH messenger RNA in the hypothalamus. The number of CRH binding sites on the other hand is reduced, possibly consequent to elevation of CRH availability.
- The number of neurons containing both CRH and vasopressin in increased and so is the number of neurons that produce vasopressin or oxytocin only. Plasma levels of arginine vasopressin (AVP) were found to be elevated in depression. Both vasopressin and oxytocin potentiate CRH-mediated ACTH release (Figure 6).
- GR binding on blood platelets and in postmortem brain is decreased, indicating that GR negative feedback is diminished.

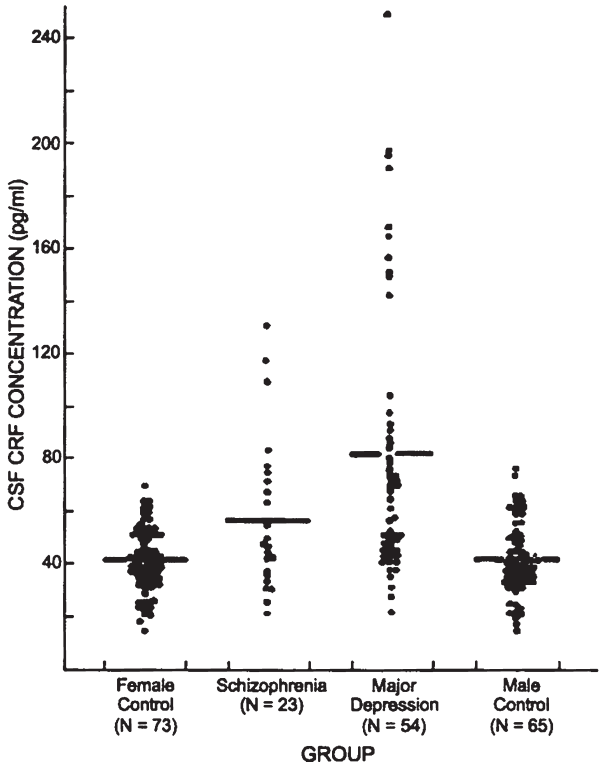


Figure 5. CSF CRF-like immunoreactivity in patients with schizophrenia, patients with major depression, and control subjects with various peripheral neurological diseases (Banki et al. 1987).

Furthermore, in depression, various *hormonal challenge tests* can be out of balance, likewise pointing to disturbed HPA axis regulation (Table II).

- First of all, the suppression of cortisol release that normally follows administration of dexamethasone may be incomplete (Carroll, 1982). Dexamethasone is a synthetic corticosteroid that like cortisol binds to GRs on ACTH producing cells in the anterior pituitary. The dexamethasone suppression test measures the capacity of GRs on the anterior pituitary to negatively control the ACTH/cortisol release. To achieve the normal degree of cortisol suppression in depressed non-suppressors, a higher dose of dexamethasone is required (Modell et al. 1997). The negative feedback acting through GRs is apparently changed to a higher setpoint.

Table II. Major disturbances in the functioning of the HPA axis in (a subtype of) depression.

Clinical findings	Challenge tests	Postmortem findings
↑ CSF CRH	Dexamethasone (Dex) non-suppression of cortisol	↑ Number CRH neurons in hypothalamus
↑ Plasma ACTH		
↑ Plasma cortisol	Blunting ACTH response to CRH	↑ CRH messenger RNA in hypothalamus
↑ Urinary cortisol		
↓ GR binding on blood platelets	Dex/CRH challenge: increased ACTH response	↑ Number vasopressin neurons in hypothalamus
Enlargement pituitary and adrenal cortex		↓ GR binding in brain

– The ACTH response to CRH may be blunted, supposedly due to downregulation of CRH receptors on the pituitary gland, secondary to overproduction of CRH (Gold et al. 1986). Blunting of the ACTH response to CRH is positively correlated with dexamethasone non-suppression (Krishnan et al. 1991).

The ACTH response to vasopressin remains normal and so does the ACTH response to a combination of CRH and vasopressin (Dinan et al. 1999). The cortisol response to a CRH challenge remains normal as well, possibly because the adrenal cortex is hyperactive and secretes more cortisol per ACTH pulse than normal (Krishnan et al. 1991). Hyperactivity of the adrenal cortex could also explain why the cortisol response to a ACTH challenge in depression might be greater than normal.

– In depressed patients, after pretreatment with dexamethasone, the ACTH response to CRH is *not* decreased, as it is in depressed patients not pretreated with dexamethasone, but rather *increased*. This has been explained in the following way (Von Bardeleben and Holsboer 1989). Dexamethasone (in low doses) does not penetrate the blood–brain barrier well. Its inhibitory effects on the HPA axis are affected predominantly by inhibiting ACTH release and not via interference with CRH release (Cole et al. 2000). ACTH and cortisol levels are thus reduced. The negative feedback on CRH release diminishes and consequently the release of CRH (and that of other ACTH-stimulating peptides such as vasopressin) will increase. An additional CRH pulse will override downregulation of the CRH receptors on the pituitary and produce an increased ACTH response. This effect will be even more pronounced in depressed patients in whom CRH and ACTH production are already elevated to begin with. (Figure 7)

Increased ACTH response to CRH after pre-treatment with dexamethasone is also found in a substantial proportion of first-degree relatives of patients with depression without a history of psychiatric illness or current stressful life events (Modell et al. 1998). Raadsheer et al. (1994, 1995) reported that hypothalamic CRH cells may remain activated in depressed patients who had been in remission.

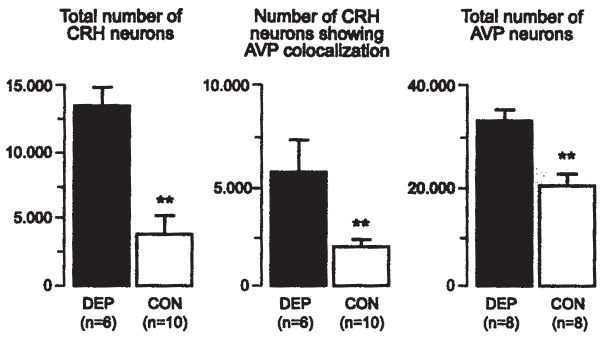


Figure 6. Number of CRH and AVP neurons in the paraventricular nucleus (PVN) of depressed patients. Patients with major depression have an increased number of CRH and arginine vasopressin (AVP) neurons and neurons containing both CRH and AVP in the hypothalamic PVN. Both peptides potentiate their actions on pituitary CRH receptors. DEP = depressed patients; CON = controls (adapted from Raadsheer et al. 1994; Purba et al. 1996; Holsboer 1999).

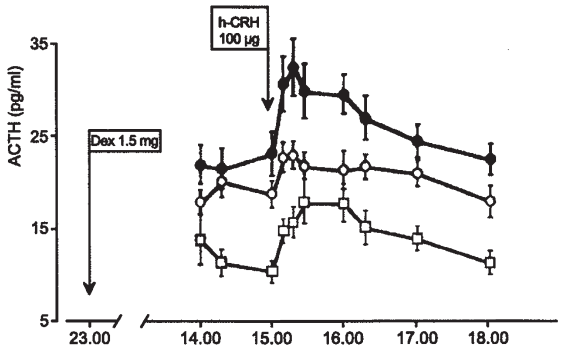


Figure 7. ACTH response to CRH after pretreatment with dexamethasone in depressed patients (●), in depressed patients after remission (○) and in normal controls (□). Relative to the control group the response in depressed patients is significantly increased. The response in the group of remitted patients is significantly lower than in the depressed phase but still greater than in the control group (after Holsboer-Trachsler et al. 1991).

Thus CRH overdrive seems to be a trait-related phenomenon.

It should be emphasized that stress hormone abnormalities are not typical for depression as such, but only occur in a subgroup of depression. These hormonal abnormalities are not specific for a subgroup of depression as presently defined either. In panic disorder, for instance, the ACTH response to CRH may be blunted (Chalmers et al. 1996) and the dexamethasone/CRH test shows alterations similar to those observable in depression (Schreiber et al. 1996). In posttraumatic stress disorders (PTSD), CSF CRH was found to be increased (Bremner et al. 1997) and in anorexia nervosa a markedly attenuated ACTH response to CRH has been reported (Chalmers et al. 1996). Apparently, the disturbances in the HPA axis are categorically non-specific and possibly related to disturbances in specific psychic regulation mechanisms, across diagnoses. It is not yet known, however, which regulatory mechanisms might be involved.

Another finding pertinent for the question under discussion – i.e. can stress cause depression – is that CRH is not restricted to the parvo-cellular division of the paraventricular nucleus, located in the hypothalamus, but in addition has a widespread extra-hypothalamic distribution. It is, for instance, found in the neocortex, amygdala, and in brainstem nuclei such as the raphe nuclei. Hypothalamic CRH controls HPA axis activity. Extra-hypothalamic CRH is a putative neurotransmitter and is held responsible for the behavioural effects of CRH.

Are the stress-hormone changes in depression, stress- or depression-related?

A major issue is whether the increased release of stress hormones is epiphenomenal or pathogenic. Pathogenic means: involved in the pathophysiology of depression. Epiphenomenal indicates that the hormonal disturbances are secondary phenomena: result of anxiety and tension that often precede and/or accompany depression. Since signs of increased HPA axis hyperactivity continue around the clock, it has been concluded that this a *primary* phenomenon and not the *resultant* of conscious upsetting experiences (Wong et al. 2000). This is not a convincing argument, because depression is often accompanied by frightening and vivid dreaming and such dreams can be pretty alarming. Several lines of evidence, however, point to stress hormones as depressogenic variables. I will discuss some of them briefly.

Stress hormones and antidepressants. Treatment with antidepressants, if effective, leads to normalization of HPA axis activity, including CSF concentration of CRH and AVP (De Bellis et al. 1999). As such, this is not an argument in support of a primary role of HPA axis overactivity. Even if overdrive of this system were to be a secondary phenomenon one would expect it to normalize after remission. Several phenomena, however, suggest a primary role of HPA axis overactivity. Various types of antidepressants, including SSRIs, noradrenaline reuptake inhibitors and monoamine oxidase inhibitors, increase: (a) corticosteroid receptor gene expression, (b) the capacity of brain tissue to bind corticosteroids and (c) steroid receptor immunoreactivity in the brain. The time course of the actions of antidepressants on corticosteroid receptor concentration, moreover, follows that of clinical improvement (Reul et al. 1993).

Rats treated with various types of antidepressants show first an increase of MRs, an effect followed by upregulation of GRs (Reul et al. 1993). Antidepressant-induced upregulation of corticosteroid receptors, particularly GRs leads to strengthening of the negative feedback and consequently to decrease of HPA axis hyperactivity with lowering of CSF CRH concentration, plasma ACTH and cortisol levels and normalization of the dexamethasone suppression test and the dexamethasone/CRH test (Zobel et al. 1999). Several SSRIs, however, do not increase GR mRNA (Seckl and Fink 1992) and, hence, upregulation of GRs cannot be considered as a unitary antidepressant mechanism.

The pronounced effects of most, but not all, antidepressants on GR gene expression support the view that hyperactivity of the CRH–ACTH–cortisol system in depression is more than just an epiphenomenon, and might be involved in the pathopysiology of (certain types of) depression.

Do CRH and cortisol influence behaviour?. CRH is a 41-amino acid peptide. High concentrations of CRH are found in the parvocellular division of the paraventricular nucleus (PVN) and in several extra-hypothalamic structures. The former division regulates the HPA axis, the latter is responsible for the behavioural components of the stress response. The behavioural effects of CRH are centrally mediated and independent of the HPA axis. They persist after hypophysectomy.

Cortisol effects CRH production. It enters the brain, diffuses passively through cell membranes, and binds to intra-cellular receptors. This process promotes their translocation to the nucleus. Within the cell nucleus the ligand-activated receptors cause up- or downregulation of the expression of various genes, amongst others those related to CRH production.

Cortisol, now, *restrains* CRH producing cells in the PVN steering the HPA axis, by inhibiting CRH gene expression. They *enhance*, however, CRH gene expression in the extrahypothalamic CRH system. Behavioural effects of CRH, thus, are not subject to the cortisol-mediated negative feedback. On the contrary, extra-hypothalamic CRH and cortisol work together in a mutually reinforcing positive feedback loop.

Behavioural effects of CRH. Administration of CRH directly into the brain, either intraventricularly or intracerebrally at specific sites leads to a wide array of behavioural effects, the character of which depends on dose and on the behavioural state of the test animal (Heinrichs et al. 1995). In animals under low arousal conditions, CRH in moderate doses produces dose-dependent behavioural activation with increased arousal and vigilance. Locomotor activity is increased, and likewise rearing, sniffing and grooming when rats are tested in a familiar environment. These effects remain after hypophysectomy, indicating that they are generated independent of the HPA axis (Eaves et al. 1985).

In higher doses, or administered to stressed animals the CRH effects are quite different and can be construed as anxiogenic. Heart rate and respiration increase and so does the blood pressure, blood sugar level, gluconeogenesis and acoustic startle response. Exploration of unfamiliar environments is decreased; stress-induced freezing is increased, and likewise the responsiveness to sensory stimuli and the conditioned fear response during aversive stimulation; sexual activity and receptivity are decreased and so is food intake while grooming is increased (Koob et al. 1993; Heinrichs et al. 1995). Plasma concentrations of adrenalin, NA, cortisol and ACTH are elevated. Whereas sympathetic nervous system is obviously activated, the parasympathetic nervous system is inhibited (de Souza 1995).

Antisense oligodeoxynucleotides against CRH or CRH receptors produce anxiolytic effects (Contarino et al. 1999). CRH antagonists also produce anxiolytic effects (Koob et al. 1993). Transgenic mice overproducing CRH were found to be 'anxious', e.g. to overrespond to novel environments (Stenzel-Poore et al. 1994). These data likewise indicate that CRH plays a role in anxiety regulation.

In non-human primates, CRH triggers anxiety/despair-related phenomena such as vocalizations, huddling and lying down behaviour, also seen after infant monkey's are separated from their mother (Owens and Nemeroff 1991; Koob et al. 1993; Arborelius et al. 1999). These effects, too, are independent of the effects of CRH on the HPA axis and are abolished or prevented by CRH receptor antagonists (Heinrichs et al. 1995).

Apparently, the regulatory significance of CRH reaches far beyond the control of the HPA axis. The effects of CRH are mediated via two receptors namely CRH_1 and CRH_2 receptors. Interestingly, recent data indicate that only activation of the CRH_1 receptor induces anxiety-related behaviour. The CRH_2 receptor seems to have opposite effects (Heinrichs et al. 1997). Knocking out this latter receptor leads to anxiety-like behaviour, suggesting that its activation might have anxiolytic effects (Kishimoto et al. 2000). A CRH-like peptide has been discovered that, like CRH, binds to both CRH_1 and CRH_2 receptors. It has been named urocortin (Vaughan et al. 1995). Its CNS distribution is distinct from CRH and it binds much stronger to CRH_2 receptors than CRH does. It, thus, seems likely that an urocortin system exist distinct from the CRH system, facilitating coping and behavioural adaptation.

In summary, CRH in animals leads to a series of stress-like physiological and behavioural phenomena. The behavioural features indicate increased anxiety, while some phenomena are also observed in animal models of depression (e.g., decreased food intake, inhibition of sexual behaviour, sleep disturbances and psychomotor activation). These data suggest a role for CRH in the pathophysiology of states of anxiety and depression, conditions that in humans often occur together.

CRH in depression. As discussed before, in depression, CRH overdrive may occur (Nemeroff et al. 1984) as is apparent from a number of observations:

- Increased CRH concentration in plasma and CSF (Nemeroff et al. 1984; Catalán et al. 1998) (Figure 7), whereas the level of CSF CRH and dexamethasone non-suppression are positively correlated.
- Serial CSF samples over 6 h revealed increased CRH levels at all time points (Baker et al. 1999).
- In post-mortem studies of depressed patients, an increase has been observed in brain CRH concentrations, CRH mRNA expression, in the number of AVP and CRH containing neurons and in those that contain both peptides (Raadsheer et al. 1994, 1995; Purba et al. 1996). Possibly secondary to increased CRH production, CRH receptor density was found to be decreased (Nemeroff et al. 1988).
- ACTH response to CRH is blunted, conceivably due to CRH receptor downregulation on the pituitary, consequent to CRH overproduction.

– Some authors did report downregulation of CRH receptors and decreased GR mRNA in the cortex of (depressed) suicide victims. Decreased GR mRNA, was also found in schizophrenia, indicating this phenomenon to be nosologically non-specific (Webster et al. 1999). Other investigators, however, found the number of CRH receptors and the affinity of CRH receptors to be unchanged (Hucks et al. 1997).

Overproduction of CRH could be a primary phenomenon (enhanced forward drive) (Nemeroff 1996) or, alternatively, the consequence of impaired GR function, leading to reduced corticoid-mediated negative feedback at the level of the pituitary corticotrope or the hypothalamus (Young et al. 1991). Some data suggest impaired feedback inhibition. Dexamethasone non-suppression, of course, is one case in point. Furthermore, GRs on lymphocytes have been found to be reduced in depressed patients (Whalley et al. 1986).

In summary, then, it appears that CRH overdrive might occur in depression, but it is by no means a universal phenomenon in this group of disorders, nor is it specific for depression. Its cause is often surmised to be downregulation of GRs, but supporting evidence is rather flimsy. Primacy of CRH overdrive remains an arguable standpoint. Interestingly, in some depressed patients CSF CRH levels were found to be *decreased* (Geracioti et al. 1997) again, suggesting that the group of mood disorders is heterogeneous in a biological sense, as it is psychopathologically.

Antagonists of stress hormones in depression. If CRH overdrive and hypercortisolemia would indeed be involved in the pathophysiology of depression or some of its components, one would expect suppression of CRH or cortisol activity to exert antidepressant effects. Indeed, antidepressants, at least some groups of antidepressants as well as lithium and electroconvulsive treatment have the ability to increase GR mRNA, to enlarge in this manner the density of GRs on the pituitary and the hypothalamic PVN and thus to strengthen the cortisol-mediated negative feedback loop (Reul et al. 1993). Presumably MRs are likewise upregulated by (some?) antidepressants (Seckl and Fink 1992), but the evidence for that is less abundant. Activation of both GRs and MRs would result in downregulation of HPA axis activity.

Recent research has focused on the development of compounds specifically capable to decrease CRH and cortisol production or to block receptors it acts on (Beverley and Murphy 1997).

Inhibitors of steroid synthesis will lower raised cortisol levels. Ketoconazole has been used for this purpose, so far particularly in patients resistant to conventional antidepressants (Ravaris et al. 1988; Wolkowitz et al. 1999b), and in addition metyrapone and aminoglutethimide (Murphy et al. 1991). Though the amount of controlled observations is still small, most investigators report encouraging results, particularly in patients with hypercortisolemia. Recently, however, Malison et al. (1999) published a negative study with ketoconazole in treatment-refractory patients with major depression.

Diminution of cortisol productions is, so it would seem, a double-edged sword. On the one hand it is expected to eliminate the noxious effects of excess cortisol, on the other hand it would weaken the cortisol-mediated brake on CRH production, a hormone supposed to play a key-role in the pathogenesis of (certain types of) depression. However, Patchev et al. (1994) demonstrated that the latter probably does not occur, since steroid synthesis inhibitors do increase the pool of neuroactive steroids and some of those suppress CRH expression.

Dehydroepiandrosterone (DHEA) and its sulphated metabolite (DHEA-S), are adrenal steroids of unknown physiological significance that possess *antiglucocorticoid properties*. DHEA is a steroid secreted by the adrenal cortex synchronously with cortisol. It may confer neuroprotection, while excess cortisol has neurotoxic potential, at least in the hippocampus (Kimonides et al. 1998). Plasma levels were found to be decreased in depression (Barrett-Connor et al. 1999). Some preliminary data suggest that DHEA might have antidepressant potential (Wolkowitz et al. 1999a). The available database, however, is not sufficient for even an interim conclusion.

Another approach to normalize cortisol levels has been the application of *type 1 CRH receptor antagonists*. In animals, such compounds reduce a repertoire of behaviours associated with anxiety (Basso et al. 1999; Arborelius et al. 2000). A recently developed compound of this nature, R 121919, a pyrazolopyrimidine derivative, is now clinically tested and seems to exert anxiolytic and antidepressant effects (Holsboer 2000, 2001; Zobel et al. 2000). It does not suppress stress-induced HPA axis activity, possibly because it leaves type-2 CRH receptors, present at the pituitary, responsive. Several other lipophilic CRH antagonists, capable of penetrating the blood–brain barrier, and possessing oral bio-availability are presently in development (Owens and Nemeroff, 1999).

Another strategy proposed to reduce circulating cortisol is *activation of GRs*, thus, strengthening the

cortisol-mediated negative feedback system. Dexamethasone has been used for this purpose in a few controlled, but small studies (Scott et al. 1999). All reported some antidepressant activity.

Finally *antagonists of GRs* have been studied. The rationale is two-fold: first, to block the detrimental effects of excess cortisol; second, to promote compensatory upregulation of GRs secondary to their blockade. This type of drug would combine antiglucocorticoid activity, and the ability to enhance the cortisol-mediated feedback on the HPA axis. Clinical experience with this type of drugs is extremely limited (McQuade and Young 2000). Only one GR antagonist – RU 4868 – has been clinically tested, and in only a few patients. The therapeutic results have been encouraging, though side effects prompted premature discontinuation of the trial (Murphy 1997). Several GR antagonists are now in development.

In summary, compounds that diminish CRH and/or cortisol activity indeed seem to have therapeutic potential in mood disorders, at least in some mood disorders. Hypercortisolemia is possibly a predictor of good response. Predictive criteria of a psychopathological nature are not yet known, nor are the risks of prolonged shortages of cortisol and/or CRH.

These observations support the view that CRH overdrive might play a role in the pathophysiology of depression.

Conclusion. Taking all data discussed in this Section together, it seems likely that overproduction of stress-hormones in depression is depression-related rather than stress-related, and that these hormones might play a role in the pathophysiology of (some types of) depression.

Interactions of the serotonergic and the stress hormone systems

The 5-HT system interacts with the various stress hormones on several levels (Table III). In this context two intersections are of particular importance: the impact of cortisol on 5-HT turnover and on the expression of particular 5-HT receptors.

Initially increased levels of plasma cortisol bring about a rise in CNS *5-HT turnover* by increasing tryptophan availability and stimulation of tryptophan hydroxylase activity (Davis et al. 1995). Sustained stress or sustained increase of plasma cortisol, however, is accompanied by diminution of 5-HT turnover (Weiss et al. 1981) and reduced 5-HT release in all areas studied, possibly due in part to activation of liver tryptophan pyrrolase activity by cortisol and increased shunting of tryptophan into the kynurenine–nicotinamide pathway (Maes and Meltzer 1995). Accordingly, an inverse relation has been found between plasma corticosterone level and 5-HT turnover in the CNS (Souza and De Loon 1986), while in depressives hypercortisolemia and prolactin response to L-tryptophan were found to be inversely correlated (Deakin et al. 1990).

Table III. CRH/cortisol–5-HT interactions.

5-HT overdrive	Sustained CRH/cortisol overdrive
↑ CRH release	↓ 5-HT turnover
↑ Cortisol release	↓ Activity of 5-HT ergic neurons
	↓ Expression 5-HT_{1A} receptors
	↓ 5-HT_{1A} receptor binding
	↑ 5-HT_2 receptor binding

The *5-HT_{1A} receptor* also responds biphasically to increased cortisol levels, initially with increased and later with decreased receptor sensitivity (Young et al. 1994; Crayton et al. 1996) and diminished expression of 5-HT_{1A} receptor mRNA (Meijer and De Kloet 1994). In accordance with this observation, hydrocortisone, in humans, reduces the growth hormone response to an infusion of L-tryptophan, a response that probably is mediated via 5-HT_{1A} receptors (Porter et al. 1998).

The cortisol and prolactin response to d-fenfluramine may be blunted in depression. After a 1-week treatment with ketoconazole, an inhibitor of cortisol synthesis, those responses normalized, irrespective whether the patient did or did not improve (Thakore and Dinan 1994). Both these observations suggest that in humans, too, corticosteroids reduce activity of the 5-HT_{1A} receptor system.

The *5-HT_2 receptor*, too, responds biphasically to hypercortisolaemia. Acute increase in plasma cortisol leads to its desensitisation (Yamada et al. 1995). Under conditions of chronic stress, 5-HT_2 receptor binding is increased (Fernandes et al. 1997). In subordinate (i.e. chronically stressed) rats, 5-HT_{1A} binding throughout the entire hippocampus was decreased, while 5-HT_2 binding in layer IV of the parietal cortex was increased (McKittrick et al. 1995).

In conclusion, then, by sustained increase of plasma cortisol the turnover of 5-HT, as well as the responsivity of the 5-HT_{1A} receptor system, is reduced. Animal data indicate upregulation of the 5-HT_2 system, but the results of human research has so far been ambiguous.

5-HT and stress hormone disturbances in depression: Conclusions

In depression, or better, in a subgroup of depression the 5-HT system may be deranged. The most prominent disturbances are a trait-related decrease

in 5-HT metabolism, a likewise trait-related down-regulation of the 5-HT_{1A} receptor system and, possibly, upregulation of the 5-HT_{2C} receptor system.

Moreover the CRH/cortisol is hyperactive, causing or aggravating the disturbances in the 5-HT system.

Behaviourally these disturbances are associated with increased anxiety (decreased 5-HT_{1A} receptor activity; increased 5-HT_{2C} receptor activity; CRH overdrive) and increased aggression (decreased 5-HT_{1A} receptor activity; cortisol overdrive).

Stress, stress hormones, and 5-HT

The central question posed in this study is whether stress may cause depression. Phrased differently, whether stress may cause brain dysfunctions supposedly underlying (certain types of) depression or certain depressive features. This question can be answered in the affirmative.

– Stress leads to CRH and cortisol overdrive. CRH release is in fact the lynchpin of the stress response. The response to adverse stimuli is a complex one, encompassing behavioural, endocrine, autonomic and immunological components. The CRH system is considered to integrate it all.

The neurosecretory cells of the parvocellular division of the PVN produce CRH. Via the projections of these cells, it is transported to the median eminence. From the nerve terminals, CRH is released into the hypothalamo–hypophyseal portal system. Via these vessels CRH is transported to the anterior pituitary, where it binds to CRH receptors on ACTH producing cells (corticotropes). Via a number of intermediary steps, this leads to increased production of pro-opiomelanocortin, the precursor molecule of peptides such as β-endorphin and ACTH. ACTH is released into the systemic circulation and triggers the release of the glucocorticoid cortisol (in men and corticosterone in rodents) by the adrenal cortex (Van Praag et al. 2004).

Activation of CRH producing cells is not limited to the hypothalamus, but occurs in the extrahypothalamic CRH-mediated systems as well.

– 5-HT metabolism is initially enhanced. Sustained stress, however will lead to diminution of the 5-HT turnover. The 5-HT_{1A} receptor system responds biphasically as well: first with increased, in the longer with decreased sensitivity. The impact of stress duration manifests itself also in the 5-HT_2 receptor system. Initially this receptor is desensitised, with continuing stress 5-HT_2 receptor binding is enhanced.

These observations were made in animals. In humans the 5-HT system has been insufficiently studied in stressed, but non-depressed individuals.

These findings demonstrate that sustained stress can cause changes in the 5-HT and CRH/cortisol systems similar to those found in a subtype of depression, and associated with instability of anxiety and aggression regulation.

The conclusion that stress may cause depression, or phrased probably more accurately, may cause particular depressive features, in particular anxiety and aggression, seems justified.

This conclusion raises the question what the clinical 'weight' is of these features, i.e. anxiety and aggression. Are they, psychopathologically speaking, just 'commoners', ordinary components of the depressive syndrome, or, alternatively, key-features, precursors as well as instigators of the depressive syndrome, true '*pacemaker symptoms*' (Van Praag, 2001a,b). This question will be raised in the last Section.

Can the depression-subtype associated with 5-HT and stress hormone disturbances be further identified?

A new subtype of depression

In the previous Sections I discussed the disturbances in the 5-HT and stress hormone systems, that have been demonstrated in 'a subtype of depression', that does not coincide with one of the depressive subtypes that are presently distinguished. Can that subtype be further specified? I think it can, at least in the mould of a hypothetical construct, that we have named '*anxiety/aggression-driven depression*'. This, still hypothetical, construct can be characterized on several levels (Van Praag 1992b, 1996a,b, 1997, 2001b).

Psychopathological characteristics

Anxiety/aggression-driven depression is heralded not by mood lowering, but by an increase in anxiety level and manifestations of enhanced outward directed aggression, such as irritability, anger outbursts with little provocation, becoming argumentative, and others.

Mood lowering is a latecomer, if it occurs at all. Some episodes remain restricted to disturbed anxiety- and aggression-regulation, in others, after some time, mood lowering does occur, in which case a full-fletched depression develops. Aggressivity and anxiety remain dominant features.

A degree of fearfulness and aggressivity not seldom persists after remission. Brody et al. (1999) demonstrated that anger, anger suppression and fear

of anger expressions, if pronounced during a depressive episode, are still demonstrable once the depression has cleared. Labile anxiety- and aggression-regulation, thus, seems to be a trait-related, personality-bound feature.

In this context we introduced the concept of '*pacemaker symptoms*', defined as disturbances in psychological control systems – in this case those responsible for anxiety- and aggression-regulation – that possess the power to disrupt others, in this case mood regulation.

Psychiatry has been accustomed placing psychopathological symptoms in a horizontal plane, failing to '*verticalize*' symptoms (Van Praag 1997b). Verticalizing symptoms means, trying to differentiate those symptoms that seem to be directly related to the pathophysiological substrate underlying a particular psychiatric syndrome, from symptoms only indirectly related to that substrate.

The concept 'pacemaker symptoms' is a particularization of the general concept 'verticalization of psychiatric symptoms' (Van Praag 1997b).

Biological characteristics

A second distinguishing mark of anxiety/aggression-driven depression is biological in nature. The chance of demonstrating diminution of 5-HT turnover is greater in this depression type than in depression with a different phenotype, and development. No data are available on possible accumulation of 5-HT receptor disturbances in this subtype of depression.

As discussed, lowering of 5-HT metabolism is a trait-related phenomenon linked to disturbances in the regulation of anxiety and aggression.

No data are as yet available on the state of the stress hormone system in this depression type.

Personality characteristics

Stress syndromes are phenomenologically heterogeneous. This fact is often ignored in stress research, much to its detriment. In particular research into the biological underpinnings of behavioural phenomena requires precise phenomenological description and differentiation. It seems unlikely that vaguely delineated syndromes will be associated with well-definable neurobiological disturbances.

Be this as it may, anxiety and (manifest or suppressed) aggression are among the features present in virtually all varieties of stress syndromes. If, therefore, the regulation of anxiety and aggression is vulnerable, in some individuals suffering from depression, one would expect them to be stress-prone, i.e. to react to (certain?) untoward experiences more readily or more vehemently than individuals in whom those regulatory systems function normal. Phrased differently, patients with anxiety/aggression-driven depression can be expected to show neurotic traits. Preliminary and tentative evidence supports this expectation.

I mention only one confirmatory observation. In a group of depressed patients with the lowest CSF 5-HIAA concentration, extracted from a cohort of 203 depressed patients, the neurosis score was significantly higher than in the 25 patients with the highest CSF 5-HIAA level.

Treatment of anxiety/aggression-driven depression

If indeed a subgroup of depression exists, in which 5-HT-related disruption of anxiety- and aggression-regulation are the driving forces, one would expect those depressions to respond preferentially to compounds that normalize the regulation of anxiety and aggression via normalization of the 5-HT-ergic and/or CRH-HPA systems. It has been hypothesized that optimal treatment of this depression type would include the following components (Van Praag 2001b).

1. Administration, not of one of the usual antidepressants, but of a selective, postsynaptic, full 5-HT_{1A} agonist. Such a compound could normalize 5-HT_{1A} receptor mediated transmission, harmonize anxiety- and aggression-regulation, and ultimately – in second instance – lead to mood normalization. Preferably this treatment should start at the stage in which only anxiety and aggression are dysregulated. In the depressive phase this intervention might be too late.

Such compounds are now on their way, so that this hypothesis can shortly be put to the test (Borsini et al. 1999). Partial, and not very selective 5-HT_{1A} receptor agonists of the azapirone group (e.g., buspirone and ipsaperone) have been shown to exert anxiolytic and antidepressive actions in humans (Deakin, 1993).

2. An antagonist or inverse agonist of 5-HT_{2A} and/or 5-HT_{2C} receptors might be considered. In humans, hyperresponsivity of this receptor system has not been convincingly demonstrated, but animal experiments indicate that this type of compound might exert anxiolytic and antidepressant effects (Sibille 1997; Yamada and Sugimoto 2001).
3. A 5-HT_{1A} agonist should be combined with a cortisol or CRH antagonist to remove the break on 5-HT (1A) receptor functioning, and to counteract the anxiogenic and depressogenic effects of CRH.

Compounds of that nature are presently being studied (Wolkowitz et al. 1999b), and thus it will be possible to evaluate this hypothesis too, in due time.

4. Psychological intervention methods should be employed to boost ego strength, improve coping abilities and unlearn inadequate adaptive reaction patterns.
5. Prophylactically a combination of pharacotherapy, with a 5-HT_{1A} agonist and/or cortisol or CRH antagonist, in combination with continued psychological treatment is indicated.

Conclusion

As was discussed previously, stress in all likelihood may *cause* depression. In this Section the question was raised whether a depression type can be identified that is particularly stress-inducible. The new construct 'anxiety/aggression-driven depression' satisfies this criterion. It is defined as a 5-HT-related depression, based on a primary dysfunction of anxiety and aggression regulation and stress-inducible per excellence. Stress-inducibility is caused by two factors: vulnerabilities in personality structure, and persistent disturbances in the 5-HT system, leading to vulnerabilities in anxiety- and aggression-regulation.

An adventitious, but still purely speculative factor could be that in the group of anxiety/aggression-driven depression individuals accumulate who are homozygous or heterozygous for the short allele version of the gene coding for the 5-HT transporter, the protein that removes 5-HT form the synaptic cleft back into the nerve ending. Caspi et al. (2003) recently demonstrated that short allele individuals respond to stressors more readily with depression than their long allele counterparts: they are in other words stress-susceptible.

Is anxiety/aggression-driven depression the only or major form of stress-inducible depression? It is not known. Further studies should clarify this matter.

The strength of the construct anxiety/aggression-driven depression in diagnostic terms, lies in the fact that it is not merely a combination diagnosis, bringing anxiety and aggression on the one hand, and depression on the other, together in a purely descriptive and horizontal way. It postulates a causal, or vertical relationship between dysfunctioning psychic domains: disturbances in anxiety- and aggression-regulation are considered primary, leading in some cases, secondarily, to disturbances in mood regulation. Furthermore, it relates those psychic dysfunctions to unassimilated psychotraumatic events, and proposes a biological interface between precipitating psychological factors and ensuing psychopathological consequences.

This type of hypothesis – cascade hypothesis, that is to say, hypotheses proposing causal relationships between psychological events, resulting brain dysfunctions and ultimately psychopathological states – is clearly needed to advance human brain and behaviour research.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Agren H, Reibring L, Hartvig P, Tedroff J, Bjurling P, Hornfeldt K, Andersson Y, Lindquist H, Langstrom B. 1991. Low brain uptake of L-[^{11}C]5-hydroxytrypyonphan in major depression: a position emission tomography study on patients and healthy volunteers. Acta Psychiatr Scand 83:449–455.

Agren H, Reibring L. 1994. PET studies of presynaptic monoamine metabolism in depressed patients and healthy volunteers. Pharmacopsychiatry 27:2–6.

Ansseau M. 1997. Hormonal disturbances in depression. In: Honig A, Van Praag HM, editors. Depression. Neurobiological, psychopathological and therapeutic advances. Chichester: John Wiley.

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. 1999. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 160:1–12.

Arborelius L, Skelton KH, Thrivikraman KV, Plotsky PM, Schulz DW, Owens MJ. 2000. Chronic administration of the selective corticotropin-releasing factor 1 receptor antagonist CP-154,526: Behavioral, endocrine and neurochemical effects in the rat. J Pharmacol Exp Ther 294:588–597.

Asberg M, Thorén P, Träskman L, Bertilsson L, Ringbergen V. 1976. Serotonin depression: A biochemical subgroup within the affective disorders? Science 191:478–480.

Audenaert K, Van Laere K, Dumont F, Slegers G, Mertens J, Van Heeringen C, Dierckx RA. 2001. Decreased frontal serotonin 5-HT_{2A} receptor binding index in deliberate self-harm patients. Eur J Nucl Med 28:175–182.

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD. 1999. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 156:585–588.

Banki CM, Bissette G, Arato M, O'Connor L, Nemeroff CB. 1987. CSF corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. Am J Psychiatry 144:873–877.

Barrett-Connor E, Von Mühlen D, Laughlin GA, Kripke A. 1999. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: The Rancho Bernado study. J Am Geriatr Soc 47:685–691.

Basso AM, Spina M, River J, Vale W, Koob GF. 1999. Corticotropin-releasing factor antagonist attenuates the anxiogenic-like effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. Psychopharmacology 145:21–30.

Benkelfat C, Ellenbogen M, Dean P, Palmour R, Young S. 1994. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. Arch Gen Psychiatry 51:687–697.

Benkelfat C, Young SN, Leyton M, Diksie M. 2002. Impulsivity: Serotonergic mechanisms. Int J Neuropsychopharmacol 5(Suppl I):S13.

Beverley E, Murphy P. 1997. Antiglucocorticoid therapies in major depression: A review. Psychoneuroendocrinology 22:S125–132.

Bhagwagar Z, Whale R, Cowen PJ. 2002. State and trait abnormalities in serotonin function in major depression. Br J Psychiatry 180:24–28.

Blier P, De Montigny C. 1994. Current advances and trends in the treatment of depression. Trends Pharm Sci 15 :220–226.

Board F, Persky H, Hamburg DA. 1956. Psychological stress and endocrine functions. Psychosom Med 18:324–333.

Borsini F, Brambilla A, Grippa N, Pitsikas N. 1999. Behavioral effects of Flibanserin (BIMT 17). Pharmacol Biochem Behav 64:137–146.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. 1997. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse: A preliminary report. Biol Psychiatry 41:23–32.

Brody CL, Haaga DA, Kirk L, Solomon A. 1999. Experiences of anger in people who have recovered from depression and never-depressed people. J Nerv Ment Dis 187:400–405.

Bromidge SM, Dabbs S, Davies DT, Davies S, Duckworth DM, Forbes IT, Gaster LM, Ham P, Jones GE, King FD, Mulholland KR, Saunders DV, Wyman PA, Blaney FE, Clarke SE, Blackburn TP, Blackburn V, Blackburn H, Kennett GA, Lightowler S, Middlemiss DN, Trail B, Riley GJ, Wood MD. 2000. Biarylcarbamoylinodolines are novel and selective 5-HT_{2C} receptor inverse agonists: identification of 5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent. J Med Chem 43:1123–1134.

Carroll BJ. 1982. The dexamethasone suppression test for melancholia. Br J Psychiatry 140 :292–304.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389.

Catalán R, Gallart JM, Castellanos JM, Galard R. 1998. Plasma corticotropin-releasing factor in depressive disorders. Biol Psychiatry 44:15–20.

Chalmers DT, Lovenberg TW, Grigoriadis DE, Behan DP, De Souza EB. 1996. Corticotrophin-releasing factor receptors: From molecular biology to drug design. Trends Pharmacol Sci 17:166–172.

Charney DS. 2004. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. Am J Psychiatry 161:195–216.

Chugani DC, Muzik O. 2000. α-[^{11}C]Methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. J Cereb Blood Flow Metab 20:2–9.

Coccaro EF. 1992. Impulsive aggression and central serotonergic system unction in humans; an example of a dimensional brain-behavior relationship. Int Clin Psychopharmacol 7:3–12.

Coccaro EF, Kavoussi RJ, Sheline YI, Berman ME, Csernansky JG. 1997. Impulsive aggression in personality disorder correlates with platelet 5-HT_{2A} receptor binding. Neuropsychopharmacology 16:211–216.

Cole MA, Kim PJ, Kalman BA, Spencer RL. 2000. Dexamethasone suppression of corticosteroid secretion: Evaluation of the site of action by receptor measures and functional studies. Psychoneuroendocrinology 25:151–167.

Contarino A, Dellu F, Koob GF, Smith GW, Lee KF, Vale W, Gold LH. 1999. Reduced anxiety-like and cognitive performance in mice lacking the corticotropin-releasing factor receptor 1. Brain Res 835:1–9.

Corrêa H, Duval F, Mokrani M-C, Bailey P, Trémeau F, Staner L, Diep T-S, Hodé Y, Crocq M-A, Macher J-P. 2000. Prolactin response to D-fenfluramine and suicidal behavior in depressed patients. Psychiatr Res 93:189–199.

Cowen PJ, Wood DJ. 1991. Biological markers of depression. Psychol Med 21:831–836.

Cowen PJ, Charig EM, Fraser S, Elliot JM. 1987. Platelet 5HT receptor binding during depressive illness and tricyclic antidepressant treatment. J Affect Disord 13:45–50.

Crayton JW, Joshi I, Gulati A, Arora RC, Wolf WA. 1996. Effect of corticosterone on serotonin and catecholamine receptors and uptake sites in rat frontal cortex. Brain Res 728:260–262.

Davis S, Heal DJ, Stanfort SC. 1995. Long-lasting effects of and acute stress on the neurochemistry and function of 5-hydroxytryptaminergic neurones in the mouse brain. Psychopharmacology 118:267–272.

Deakin JFW. 1993. A review of clinical efficacy of 5-HT_{1A} agonists in anxiety and depression. J Psychopharmacol 7:283–289.

Deakin JFW, Pennell I, Upadhyaya AJ, Lofthouse R. 1990. A neuroendocrine study of 5-HT function in depression: Evidence for biological mechanisms of endogenous and psychosocial causation. Psychopharmacology 101:85–92.

De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND. 1999. Developmental traumatology part I: Biological stress systems. Biol Psychiatry 45:1259–1270.

De Kloet ER. 1991. Brain corticosteroid receptor balance and homeostatic control. Front Neuroendocrinol 12:95–164.

De Kloet ER, Reul JM. 1987. Feedback action and tonic influence of corticosteroids on brain function: A concept arising from the heterogeneity of brain receptor systems. Psychoneuroendocrinology 12:83–105.

Delgado P, Moreno F. 2000. Role of norepinephrine in depression. J Clin Psychiatry 61(Suppl):5–12.

Delgado PL, Charney DS, Price LH, Landis H, Heninger GR. 1989. Neuroendocrine and behavioral effects of dietary tryptophan restriction in healthy subjects. Life Sci 45:2323–2332.

De Souza EB. 1995. Corticotropin-releasing factor receptors: Physiology, pharmacology, biochemistry and role in central nervous system and immune disorders. Psychoneuroendocrinology 20:789–819.

D'Haenen H, Bossuyt A, Mertens J, Bossuyt-Piron C, Gijsemans M, Kaufman L. 1992. SPECT imaging of serotonin2 receptors in depression. Psychiatr Res Neuroimaging 45:227–237.

Diksic M, Nagahiro S, Sourkes TL, Yamamoto YL. 1990. A new method to measure brain serotonin synthesis in vivo, I: Theory and basic data for a biological model. J Cereb Blood Flow Metab 10:1–12.

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C. 1999. PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 46:1375–1387.

Eaves M, Britton KT, Rivier J, Vale W, Koob GF. 1985. Effects of corticotropin releasing factor on locomotor activity in hypophysectomized rats. Peptides 6:923–926.

Fernandes C, McKittrick CR, File SE, McEwen BS. 1997. Decreased 5- HT_{1a} and increased 5-HT_{2a} receptor binding after chronic corticosterone associated with a behavioural indication of depression but not anxiety. Psychoneuroendocrinology 22:477–491.

Florey JD, Mann JJ, Manuck SB, Muldoon MF. 1998. Recovery from major depression is not associated with normalisation of serotonergic function. Biol Psychiatry 43:320–326.

Geracioti TD, Loosen PT, Orth DN. 1997. Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. Biol Psychiatry 42:166–174.

Germine M, Goddard AW, Woods CW, Charney DS, Heninger GR. 1992. Anger and anxiety responses to m-chlorophenylpiperazine in generalized anxiety disorder. Biol Psychiatry 32:457–461.

Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese IR, Kellner CH, Nieman LK, Post RM, Pickar D, Gallucci W, Avgerinos P, Paul S, Oldfield EH, Cutler GB, Chrousos GP. 1986. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease: Pathophysiologic and diagnostic implications. New Engl J Med 314:1329–1335.

Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R. 2002. Serotonin1A receptor acts during development to establish normal anxiety-like behavior in the adult. Nature 416:396–400.

Heinrichs SC, Menzaghi F, Merlo Pich E, Britton KT, Koob GF. 1995. The role of CRF in behavioral aspects of stress. Ann NY Acad Sci 771:92–104.

Heinrichs SC, Lapsansky J, Lovenberg TW, De Souza EB, Chalmers DT. 1997. Corticotropin-releasing factor CRF1, but not CRF2, receptors mediate anxiogenic-like behaviour. Regul Peptides 71:15–21.

Holsboer F. 1999. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. Psychiatr Res 33:181–214.

Holsboer F. 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23:477–501.

Holsboer F. 2001. Stress, hypercortisolism and corticosteroid receptors in depression: Implications for therapy. J Affect Disord 62:77–91.

Holsboer-Trachsler E, Stohler R, Hatzinger M. 1991. Repeated administration of the combined dexamethasone human corticotropin releasing hormone stimulation test during treatment of depression. Psychiatr Res 38:163–171.

Hrdina PD, Demeter E, Vu TB, Sotonyi P, Palkovits M. 1993. 5-HT uptake sites and 5-HT_2 receptors in brain of antidepressant-free suicide victims/depressives: increase in 5-HT_2 sites in cortex and amygdale. Brain Res 614:37–44.

Hucks D, Lowther S, Rufus Crompton M, Katona CLE, Horton RW. 1997. Corticotropin-releasing factor binding sites in cortex of depressed suicides. Psychopharmacology 134:174–178.

Joëls M, De Kloet E. 1994. Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. Prog Neurobiol 43:1–36.

Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J. 1998. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DH-EAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. Proc Natl Acad Sci USA 95:1852–1857.

Kishimoto T, Radulovic J, Radulovic M, Lin CR, Schrick C, Hooshmand F, Hermanson O, Rosenfeld MG, Spiess J. 2000. Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. Nat Genet 24:415–419.

Klaassen T, Riedel WJ, Van Someren A, Deutz NEP, Honig A, Van Praag HM. 1999a. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. Biol Psychiatry 46:489–497.

Klaassen T, Riedel WJ, Deutz NEP, Van Someren A, Van Praag HM. 1999b. Specificity of the tryptophan depletion method. Psychopharmacology 141:279–286.

Koob GF, Heinrichs SC, Pich EM, Menzaghi F, Baldwin H, Miczek K, Britton KT. 1993. The role of corticotropin-releasing factor in behavioural responses to stress. In: De Souza EB, Nemeroff CB, editors. Corticotropin-releasing factor: Basic and clinical studies of a neuropeptide. Chichester: John Wiley & Sons.

Krishnan KRR, Doraiswamy PM, Lurie SN, Figiel GS, Husain MM, Boyko OB, Ellinwood EH, Nemeroff CB. 1991. Pituitary size in depression. J Clin Endocrinol Metab 72:256–259.

Lesch KP, Mayer S, Disselkamp-Tietze Hoh A, Wiesmann M, Osterheider M, Schulte HM. 1990. 5-HT_{1a} receptor responsivity in unipolar depression: Evaluation of ipsapirone-induced ACTH and cortisol secretion in patients and controls. Biol Psychiatry 28:620–628.

Leyton M, Okazawa H, Diksic M, Paris J, Rosa P, Mzengeza S, Young S, Blier P, Benkelfat C. 2001. Brain regional α-[^{11}C]Metyl-L-Tryptophan trapping in impulsive subjects with borderline personality disorder. Am J Psychiatry 158:775–782.

Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. 1983. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non impulsive violent behaviour. Life Sci 33:2609–2619.

Maes M, Meltzer H. 1995. The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: The fourth generation of progress. New York: Raven Press.

Maes M, Jacobs M.P, Suy E, Minner B, Leclercq C, Christiaens F, Raus J. 1990. Suppressant effects of dexamethasone on the availability of plasma l-tryptophan and tyrosin in healthy controls and in depressed patients. Acta Psychiatr Scand 81:19–23.

Malison RT, Anand A, Pelton GH, Kirwin P, Carpenter L, McDougle CJ, Heninger GR, Price LH. 1999. Limited efficacy of ketoconazole in treatment-refractory major depression. J Clin Psychopharmacol 19:466–470.

Mayorga A, Dalvi A, Page M, Zimov-Levinson S, Hen R, Lucki I. 2001. Antidepressant-like behavioral effects in 5-hydroxytryptamine1A and 5-hydroxytryptamine1B receptor mutant mice. J Pharmacol Exp Ther 298:1101–1107.

McKittrick CR, Blanchard DC, Blanchard RJ, McEwen BS, Sakai RR. 1995. Serotonin receptor binding in a colony model of chronic social stress. Biol Psychiatry 37:383–393.

McQuade R, Young AH. 2000. Future therapeutic targets in mood disorders: The glucocorticoid receptor. Br J Psychiatry 177:390–395.

Meijer OC, De Kloet ER. 1994. Corticosterone suppresses the expression of 5-HT_{1a} receptor mRNA in rat dentate gyrus. Eur J Pharmacol Mol Pharm Sect 266:255–261.

Meyer JH, Kapur S, Houle S, DaSilva J, Owczarak B, Brown GM, Wilson AA, Kennedy SH. 1999. Prefrontal cortex 5-HT_2 receptors in depression: An [18F]Setoperone PET imaging study. Am J Psychiatry 156:1029–1034.

Mignot E, Seffano A, Laude D, Elghozi JL, Dedek J, Scatton B. 1985. Measurement of 5-HIAA levels in ventricular CSF (by LCEC) and in striatum (by in vivo voltametry) during pharmacological modification of serotonin metabolism in the rat. J Neural Transm 62:117–124.

Modell S, Yassouridis A, Huber J, Holsboer F. 1997. Corticosteroid receptor function is decreased in depressed patients. Neuroendocrinology 65:216–222.

Modell S, Lauer CJ, Schreiber M, Huber J, Krieg JC, Holsboer F. 1998. Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. Neuropsychopharmacology 18:253–262.

Moja E, Cipolla P, Castoldi D, Tofanetti O. 1989. Dose-response decrease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino acid mixtures in rats. Life Sci 44:971–976.

Murphy BEP. 1997. Antiglucocorticoid therapies in major depression: A review. Psychoneuroendocrinology 22:S125–132.

Murphy BEP, Dhar V, Ghadirian AM, Chouinard G, Keller R. 1991. Response to steroid suppression in major depression resistant to antidepressant therapy. J Clin Psychopharmacol 11:121–126.

Nemeroff CB. 1996. The corticotropin-releasing factor hypothesis of depression: New findings and directions. Mol Psychiatry 1:336–342.

Nemeroff CB, Widerlöv E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W. 1984. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226:1342–1344.

Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. 1988. Reduced corticotropin-releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry 45:577–579.

Newman ME, Shapira B, Lerer B. 1998. Evaluation of central serotonergic function in affective and related disorders by the fenfluramine challenge test: A critical review. Int J Neuropsychopharmacology 1:49–69.

Owens MJ, Nemeroff CB. 1991. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev 43:425–473.

Owens MJ, Nemeroff CB. 1999. Corticotropin-releasing factor antagonists. CNS Drugs 12:85–92.

Pandey GN, Pandey SC, Janicak PG, Marks RC, Davis JM. 1990. Platelet serotonin receptor binding sites in depression and suicide. Biol Psychiatry 28:215–222.

Parks C, Robinson P, Sibille E, Shenk Th, Toth M.. 1998. Increased anxiety of mice lacking the serotonin1A receptor. Proc Natl Acad Sci USA 95:10734–10739.

Patchev VK, Shoaib M, Holsboer F, Almeida OF. 1994. The neurosteroid tetrahydroprogesterone counteracts corticotropin-releasing hormone-induced anxiety and alters the release and gene expression of corticotropin-releasing hormone in the rat hypothalamus. Neuroscience 62:265–271.

Porter R, McAllister-Williams RH, Lunn B, Young A. 1998. 5-Hydroxytryptamine receptor function in man is reduced by acute administration of hydrocortisone. Psychopharmacology 139:243–250.

Purba JS, Hoogendijk WJG, Hofman MA, Swaab DF. 1996. Increased number of vasopressin neurons in the paraventricular nucleus of the human hypothalamus in depression. Arch Gen Psychiatry 53:137–143.

Raadsheer FC, Hoogendijk WJG, Hofman MA, Swaab DF. 1994. Increased numbers of corticotropin-releasing hormone neurons in the hypothalamic-paraventricular nucleus of depressed patients. Clin Neuroendocrinol 60:436–444.

Raadsheer FC, Van Heerikhuize JJ, Lucassen PJ, Hoogendijk WJ, Tilders FJ, Swaab DF. 1995. Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. Am J Psychiatry 152: 1372–1376.

Ravaris CL, Sateia MJ, Beroza KW, Noordsy DL. 1988. Effect of ketoconazole on a hypophysectomized, hypercortisolemic, psychotically depressed woman. Arch Gen Psychiatry 45: 966–967.

Redrobe JP, Mac Sweeney CP, Bourin M. 1996. The role of 5-HT_{1A} and 5-HT_{1B} receptors in antidepressant drug actions in the mouse forced swimming test. Eur J Pharmacol 318:213–230.

Reul JM, Stec I, Soder M, Holsboer F. 1993. Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic-pituitary-adrenocortical system. Endocrinology 133:312–320.

Riedel WJ, Klaassen T, Griez E, Honig A, Menheere PPCA, Van Praag HM. 2002. Dissociable hormonal, cognitive and mood responses to neuroendocrine challenge: Evidence for receptor-specific serotonergic dysregulation in depressed mood. Neuropsychopharmacology 26:358–367.

Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF. 1973. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 28:19–24.

Sandou F, Aimara DA, Dierick A, Le Meur M, Ramboz S, Segu L, Buhot M, Hen R. 1994. Enhanced agressive behavior in mice leacking 5-HT_{1B} receptors. Science 265:1875–1878.

Sargent PA, Husted Kjaer K, Bench ChrJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PhJ. 2000. Brain serotonin 1A receptor binding measured by positron emission tomography with [^{11}C]WAY-100635. Effects of depression and antidepressant treatment. Arch Gen Psychiatry 57:174–180.

Schreiber W, Lauer CJ, Krumrey K, Holsboer F, Krieg JC. 1996. Dysregulation of the hypothalamic-pituitary-adrenocortical system in panic disorder. Neuropsychopharmacology 15:7–15.

Scott LV, Thakore J, Burnett F, Dinan TG. 1999. A preliminary study of dexamethasone treatment on pituitary-adrenal responsivity in major depression. Hum Psychopharmacol Clin Exp 14:587–591.

Seckl JR, Fink G. 1992. Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo. Neuroendocrinology 55:621–626.

Sibille E, Sarnyai Z, Benjamin D, Gal J, Baker H, Toth M. 1997. Antisense inhibition of 5-hydroxytryptamine 2A receptor induces an antidepressant effect in mice. J Pharmacol Exp Ther 52:1056–1063.

Souza EB, De Loon GR. 1986. Brain serotonin and catecholamine responses to repeated stress in rats. Brain Res 367:77–86.

Stanley M, Traskman L, Dorovine K. 1985. Correlation between aminergic metabolites simultaneously obtained from human CSF and brain. Life Sci 37:1279–1286.

Stenzel-Poore MP, Heinrichs SC, Rivest S, Koob GF, Vale WW. 1994. Overproduction of corticotropin-releasing factor in transgenic mice: A genetic model of anxiogenic behaviour. J Neurosci 14:2579–2584.

Thakore JH, Dinan TG. 1994. d-Fenfluramine-induced prolactin release in depression: The acute effects of ketoconazole. J Seroton Res 3:7–213.

Träskman-Bendz L, Åsberg M, Bertilsson L, Thorén P. 1984. CSF monoamine metabolites of depressed patients during illness and after recovery. Acta Psychiatr Scand 69:333–342.

Van Praag HM. 1969. Depressie en de stofwisseling van 5-hydroxytryptamine (Depression and the metabolism of 5-hydroxytryptamine). Ned Tijdschr Geneesk (Dutch Med J) 113:2245–2247.

Van Praag HM. 1977. Significance of biochemical parameters in the diagnosis, treatment and prevention of depressive disorders. Biol Psychiatry 12:101–131.

Van Praag HM. 1988. Serotonergic mechanisms and suicidal behaviour. Psychiatr Psychobiol 3:335–346.

Van Praag HM. 1992a. Make believes in psychiatry or the perils of progress. New York: Brunner Mazel.

Van Praag HM. 1992b. About the centrality of mood lowering in mood disorders. Eur Neuropsychopharmacol 2:393–404.

Van Praag HM. 1996a. Serotonin–related, anxiety/aggression-driven, stressor-pecipitated depression. A psychobiological hypothesis. Eur Psychiatry 11:57–67.

Van Praag HM. 1996b. Faulty cortisol/serotonin interplay. Psychopathological and biological characterisation of a new hypothetical depression subtype (SeCa depression). Psychiatr Res 65:143–157.

Van Praag HM. 1997a. Demoralization and melancholy: Concerning the biological interface between traumatic life experiences and depression. In: Honig A, Van Praag HM, editors.

Depression: Neurobiological, psychopathological and therapeutic advances. Chichester: John Wiley & Sons Ltd.

Van Praag HM. 1997b. Over the mainstream: Diagnostic requirements for biological psychiatric research. Psychiatr Res 72:201–212.

Van Praag HM. 2000. Nosologomania, a disorder of psychiatry. World J Biol Psychiatry 1:151–158.

Van Praag HM. 2001a. Historical and contemporary notes on the treatment of depression, or, How classification shaped therapeutic approaches. In: Den Boer JA, Westenberg HGM, editors. Antidepressants: selectivity or multiplicity?. Amsterdam: Benecke.

Van Praag HM. 2001b. Anxiety/aggression-driven depression. A paradigm of functionalization and verticalization of psychiatric diagnosis. Prog Neuro-Psychopharmacol Biol Psychiatry 25:893–924.

Van Praag HM, Korf J. 1971. Endogenous depressions with and without disturbances in the 5-hydroxytryptamine metabolism: A biochemical classification? Psychopharmacology 19:148–152.

Van Praag HM, Korf J, Puite J. 1970. 5-Hydroxindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. Nature 225:1259–1260.

Van Praag HM, De Haan S. 1980a. Central serotonin deficiency. A factor which increases depression vulnerability? Acta Psychiatr Scand 61:89–95.

Van Praag HM, De Haan S. 1980b. Depression vulnerability and 5-hydroxytryptophan prophylaxis. Psychiatr Res 3:75–83.

Van Praag HM, Kahn R, Asnis GM, Wetzler S, Brown S, Bleich A, Korn M. 1987. Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. J Affect Disord 13:1–8.

Van Praag HM, De Kloet F, Van Os J. 2004. Stress, the brain and depression. Cambridge: Cambridge University Press.

Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy D, Rivier C, Rivier J, Sawchenko PE, Vale W. 1995. Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. Nature 378:287–292.

Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, Nemeroff C, Bissette G, Kalogeras K, Karonen SL, Linnoila M. 1994. CSF biochemistries, glucose metabolism and diurnal activity rhythms in alcoholic violent offenders, fire setters and healthy volunteers. Arch Gen Psychiatry 51:20–27.

Von Bardeleben U, Holsboer F. 1989. Cortisol response to a combined dexamethasone-hCRH challenge in patients with depression. J Neuroendocrinol 1:485–488.

Weiss JM, Goodman PA, Losito BG, Corrigan S, Charry JM, Bailey WH. 1981. Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. Brain Res Rev 3:167–205.

Whale R, Clifford EM, Bhagwagas Z, Cowen PhJ. 2001. Decreased sensitivity of 5-HT_{1D} receptors in melancholic depression. Br J Psychiatry 178:454–457.

Whalley LJ, Borthwick N, Copolov D, Dick H, Christie JE, Fink G. 1986. Glucocorticoid receptors and depression. Br Med J 292:859–861.

Williams WA, Shoaf SE, Hommer D, Rawlings R, Linnoila M. 1999. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. J Neurochem 72:1641–1647.

Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Breier A, Doran A, Rubinow D, Pickar D. 1999a. Treatment of depression with antiglucocorticoid drugs. Psychosom Med 61:698–711.

Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Breier A, Doran A, Rubinow D, Pickar D, Chan T, Knutson B. 1999b. Antiglucocorticoid treatment of depression: Double-blind ketoconazole. Biol Psychiatry 45:1070–1074.

Wong M-L, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, Karp B, McCutcheon LE, Geracioti TD, DeBellis MD, Rice KC, Goldstein DS, Veldhuis JD, Chrousos GP, Oldfield EH, McCann SM, Gold PW. 2000. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercorticoslism and corticotropin-releasing hormone. Proc Natl Acad Sci USA 97:325–330.

Yamada J, Sugimoto Y. 2001. Effects of 5-HT_2 receptor antagonists on the anti-immobility effects of imipramine in the forced swimming test with mice. Eur J Pharmacol 427:221–225.

Yamada S, Watanbe A, Nankai M, Toru M. 1995. Acute immobilization stress reduces (±)DOI-induced 5-HT_{2a} receptor-mediated head shakes in rats. Psychopharmacology 119:9–14.

Yatham LN, Liddle PF, Dennie JL, Shiah I, Adam MJ, Lane CJ, Lam RW, Ruth ThJ. 1999. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment. Arch Gen Psychiatry 56:705–711.

Yatham LN, Liddle PF, Shiah I-S, Scarrow G, Lam RW, Adam MJ, Zis AP, Ruth TJ. 2000. Brain serotonin2 receptors in major depression. A positron emission tomography study. Arch Gen Psychiatry 57:850–858.

Young S, Smith S, Pihl R, Ervin F. 1985. Tryptophan depletion cases a rapid lowering of mood in normal males. Psychopharmacology (Berlin) 87:173–177.

Young EA, Haskett RF, Murphy-Weinberg V, Watson SJ, Akil H. 1991. Loss of glucocorticoid fast feedback in depression. Arch Gen Psychiatry 48:693–699.

Young AH, Goodwin GM, Dick H, Fink G. 1994. Effects of glucocorticoids on 5-HT_{1a} presynaptic function in the mouse. Psychopharmacology 114:360–364.

Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. 2000. Hormonal evidence for altered responsiveness to social stress in major depression. Neuropsychopharmacology 23: 411–418.

Zobel AW, Yassouridis A, Frieboes RM, Holsboer F. 1999. Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. Am J Psychiatry 156:949–951.

Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. 2000. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 34:171–181.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 23–30

LECTURE

Some biological correlates of drug resistance in schizophrenia: A multidimensional approach

A. CARLO ALTAMURA, ROBERTA BASSETTI, ELISABETTA CATTANEO & SERENA VISMARA

Department of Psychiatry, University of Milan, Hospital 'Luigi Sacco', Milan, Italy

Abstract

Drug resistance in schizophrenic disorders treated with an antipsychotic medication is highly problematic, lacking sound criteria to define it, and to discriminate between drug response and clinical remission. This article reviews some neurochemical, psychoimmunological, pharmacogenetic and neuromorphological patterns which can affect drug response and determine drug-resistance phenomena in schizophrenia. Several neurochemical abnormalities have been reported to be relevant for the pathogenesis of schizophrenic disorders and have been related to clinical symptoms as well as to the quality of response to antipsychotics: most of the findings come from studies on DA and 5HT brain metabolism, but more recently other non-dopaminergic pathways have been implicated (e.g., glutamatergic ones). Literature data suggest that schizophrenia may be associated with significant alterations of T-cell functions, showing the activation of the inflammatory response system (IRS), particularly in treatment-resistant schizophrenia, and differential effects on IRS have been reported for conventional and atypical antipsychotics. Furthermore molecular genetic approaches provide a novel method of dissecting the heterogeneity of psychotropic drug response, providing the means of determining the molecular substrates of drug efficacy and drug-induced adverse events. On the other hand, functional neuroimaging techniques, including single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (FMRI), providing an *in vivo* assessment of the expression and function of neuroreceptors, transporters and enzymes, seem to be particularly promising for a better understanding of 'real' drug resistance. Finally, a multidimensional approach taking into account all these variables in the future would likely be the more valuable strategy to optimise response, reducing relapses or resistant clinical situations.

Key words: *Schizophrenia, antipsychotic treatment, drug-resistance, pharmacogenetics*

Introduction

Defining treatment resistance among patients suffering from schizophrenia is highly problematic since most of them experience persistent morbidity over the course of their illness and full remissions are infrequent (Sheitman and Lieberman 1998). There is no univocal definition of drug resistance (Pantelis and Lambert 2003): the most stringent definition of treatment resistance in schizophrenia has been developed by Kane et al. (1988), it defines refractoriness as persisting positive psychotic symptoms despite at least three treatment periods with neuroleptic drugs (from at least two chemical classes) of at least 6 weeks within the last 5 years at doses equivalent to 1,000 mg/day of chlorpromazine.

In general, from a clinical perspective, there are some other aspects which deserve to be carefully considered in order to assess the type, degree and possible causal determinants of drug resistance in schizophrenia.

Firstly it is necessary to make a distinction between full versus partial drug response in schizophrenic patients receiving an antipsychotic treatment.

Full response is usually defined as at least 40% of amelioration of the basal total score on psychiatric rating scales such as the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Symptoms Scale (PANSS) (Breier et al. 1994).

On the other hand, partial response is a very usual phenomenon and is defined as persistent symptoms while previously taking therapeutic doses of an antipsychotic: Emsley et al. (2000) suggested considering partial response as a total score of at least 15

Correspondence: A. Carlo Altamura, Chair of Psychiatry, Department of Clinical Sciences 'Luigi Sacco', University of Milan, Via G.B. Grassi 74, 20157 Milan, Italy. Tel: +39 2390 42904. Fax: +39 2390 42510. E-mail: c.altamura@hsacco.it

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030027

on PANSS, with a score for one or more of items like delusions, conceptual disorganization, hallucinatory behaviour, suspiciousness/persecution, and a score ≥ 3 on CGI 'severity of illness'.

However, full response does not mean remission of symptoms and it appears to be a more complex criterion (as for mood and anxiety disorders).

Traditionally, remission criteria in non-psychiatric disorders have been characterized by the disappearance of symptoms. In the case of chronic and progressive illnesses with psychiatric and non-psychiatric components, consensus of remission as an absence of symptoms has not been achieved. To date, remission in mental disorders (such as anxiety) has been defined not by the complete absence of anxious or depressive symptoms, but rather by minimal symptoms with mild disability (Doyle and Pollack 2003). While the symptoms of many anxiety and depressive disorders co-exist with normal life experience, the commonly recognized symptoms of schizophrenia (e.g., delusions or hallucinations) lie outside this experience. This observation may be confounding when defining 'remission' in major psychoses (Andreasen et al. 2005).

In schizophrenia, the cycle of relapse produces incomplete or unsustained symptom remission in many patients: this may subsequently lead to chronic illness characterized by substantial morbidity and persistent deficits in cognition and psychosocial function, referred often as 'refractory' schizophrenia (Lieberman et al. 2001).

Recently, Practice Guidelines developed by the American Psychiatric Association recognized a three-phase model of schizophrenia disease course, in which phases 'merge into one another without absolute, clear boundaries between them' (APA 1997). In this model, the 'acute phase', characterized by florid psychosis and severe positive and/or negative symptoms, is followed by a 'stabilization phase', during which symptoms ameliorate and become less severe, and a following 'stable phase', characterized by reduced symptoms severity and relative clinical stability. According to APA Guidelines, 'the majority of patients alternate between acute psychotic episodes and stable phases with full or partial remission' (APA 1997); however, the operational criteria for remission remain undefined.

Another important aspect which may be considered is the quality of the response. In this perspective, a 'dimensionalistic' approach could be useful, even when defining drug response, since a different role for specific psychopathological dimensions in determining the efficacy of pharmacological treatments could be hypothesized. Three dimensions have been identified using statistical techniques of factor analysis. The first, the negative symptom dimension, includes poverty of speech, decreased spontaneous movement, unchanging facial expression, paucity of expressive gesture, affective non-response, and lack of vocal inflection. The second, the disorganization dimension, includes symptoms of inappropriate affect, poverty of content of speech, tangentiality, derailment, pressure of speech, and distractibility. The third, the psychoticism dimension, includes hallucinations and delusional ideas. The validity of these dimensions has been supported by studies demonstrating relationship with neuropsychological, clinical outcome, and neuroimaging patterns (Bilder et al. 1985; Liddle et al. 1992; Arndt et al. 1995; Andreasen and Olsen 1982). However, it is important to ascertain whether the poor or non-response is related to all these dimensions or only to one of them.

Finally, the difference between 'real' and 'pseudo' drug resistance needs to be considered. In general, heterogeneity of schizophrenia in terms of clinical history (age of onset, duration of illness, familial versus non-familial forms, etc.), symptoms (e.g., positive versus negative ones), and some biological factors, are responsible for the 'real' resistance. On the other hand, the 'pseudo' or 'apparent' drug resistance phenomena are not due to the lack of a pharmacodynamic action of the compound, but are influenced by other clinical and pharmacological variables, such as incorrect diagnosis, concomitant organic disorders, inadequate dosage or duration of pharmacological treatment or poor compliance (Altamura 1990; 1992).

This review focuses on some neurochemical, psychoimmunological, pharmacogenetic and neuromorphological patterns which can influence drug response and contribute or determine drug resistance phenomena in schizophrenia.

Neurochemical factors

Neurochemical abnormalities in schizophrenic patients have been implicated in the pathogenesis and clinical symptoms, as well as in response to antipsychotic treatment. Most of the findings from studies on neurochemical factors concern DA and 5HT brain metabolism. In particular, plasma and CSF levels of monoamine precursors and/or metabolites have been used as a peripheral measure of central dopaminergic and serotonergic activity.

A relationship of plasma free homovanillic acid (pHVA) to treatment response in schizophrenia has been reported (Bowers et al. 1984; Mazure et al. 1991; Garver et al. 2000; Kim et al. 2000): all these studies demonstrated that elevated pre-treatment pHVA was significantly associated with good treatment response, and that treatment with conventional

antipsychotics appeared to be correlated with a lowering of pHVA levels.

Szymanski et al. (1993) measured DA and 5-HT plasma and CSF metabolites and the relationship of these values to clinical response to clozapine in 19 neuroleptic refractory and intolerant schizophrenic patients. Only few changes in the CSF and plasma homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) levels were found. However, the pretreatment CSF HVA/5-HIAA ratio and, to a lesser extent, the CSF HVA level predicted treatment response. These findings were replicated in some subsequent studies (Kahn et al. 1993; Lieberman et al. 1994; Wieselgren and Lindstrom 1998).

Another study, focused on the efficacy and mechanisms of risperidone towards positive symptoms in the acute phase of schizophrenia, found that higher levels of plasma HVA before risperidone administration seem to be predictive of a good response to the antipsychotic (Yoshimura et al. 2003). In a recent study, Van der Heijden et al. (2004) investigated the effect of atypical antipsychotics (olanzapine, sertindole, and quetiapine) on monoaminergic metabolites (5-HT, HVA, 5-HIAA, and HVA/5-HIAA ratio) in 66 schizophrenic patients and 73 healthy controls. The AA found that 5-HT plasma and platelet concentration was significantly lower in schizophrenic patients with poor response to atypical antipsychotics, and increased significantly during treatment, whereas no differences in plasma HVA, 5-HIAA, and their ratios, were observed between controls and response group. On the other hand, olanzapine appeared to increase HVA concentrations and the HVA/5-hydroxyindolacetic acid (5-HIAA) ratio in CSF of schizophrenic patients, but these changes were unrelated to its clinical efficacy (Scheepers et al. 2001).

A disturbance in glutamatergic neurotransmission has been hypothesized in schizophrenia, particularly influencing treatment response of negative symptoms. The beneficial effects of pharmacological treatment on these 'nuclear' schizophrenic symptoms may be related to adaptive changes taking place in these pathways (Tascedda et al. 2001). Although currently used antipsychotics do not interact with glutamatergic receptors, previous studies have demonstrated that the expression profile of ionotropic glutamate receptors can be regulated by drugs such as haloperidol or clozapine. The mRNA levels for NMDA and AMPA receptor subunits were measured after chronic treatment with quetiapine and compared to haloperidol and clozapine treatment (Tascedda et al. 1999). Similarly to clozapine, quetiapine reduced mRNA expression for NMDA subunits in the nucleus accumbens. Furthermore quetiapine, but not haloperidol or clozapine, increased the hippocampal expression for specific AMPA subunits, suggesting that the differences between typical and atypical antipsychotics may be relevant for their therapeutic activity and could provide information for the role of glutamate on specific schizophrenic symptoms. Moreover, in preclinical studies, chronic but not acute exposure to olanzapine up-regulated hippocampal mRNA levels for AMPA subunits (Tascedda et al. 2001). This effect could be relevant for the improvement of schizophrenic symptoms which are thought to depend on dysfunctioning of glutamatergic transmission.

In the above-mentioned study from Van der Heijden et al. (2004), the effect of atypical antipsychotics was examined also in relation to glutamatergic neurotransmission, showing that treatment with these compounds coincided with a significant enhancement of glutamatergic neurotransmission.

Psychoimmunological factors

Some evidence seems to show that the neuroimmune–endocrine cross-talk may be impaired in schizophrenia (Altamura et al. 1999; Boin et al. 2001). In particular, schizophrenia has been associated with several immunological changes, including decreased mitogen-induced lymphocyte proliferation (Chengappa et al. 1995), altered numbers of total T-cells and T-helper cells (Muller et al. 1993), the presence of antibrain antibodies in serum (Henneberg et al. 1994), and changes in cytokines and cytokine receptors in the blood and the cerebrospinal fluid (CSF) (Licinio et al. 1993; Ganguli et al. 1994, 1995; Rapaport et al. 1994, 1997; Maes et al. 1995, 1997, 2000, 2002; Lin et al. 1998; Arolt et al. 2000; Zhang et al. 2002a, 2002b). All these data suggest that schizophrenia may be associated with significant immunological alterations in parallel with impaired T-cell functions, showing the activation of the inflammatory response system (IRS), particularly in treatment-resistant schizophrenia (Lin et al. 1998; Maes et al. 2000, 2002).

Other evidence supported the hypothesis that in schizophrenia a dysfunction of the HPA axis could be present (Walker and Diforio 1997; Marx and Lieberman 1998). In fact, dexamethasone suppression test (DST) non-suppression, due to the lack of glucocorticoid secretion feedback mechanisms, occurs frequently in schizophrenia, with percentages varying between 11 and 55% (Sharma et al. 1988; Altamura et al. 1989; Yeragani 1990; Coryell and Tsuang 1992). Moreover, other studies showed that basal cortisol levels were significantly higher in schizophrenic patients than in normal controls (Altamura et al., 1989; Lammers et al. 1995; Walker

and Diforio 1997), although these findings are not univocally observed in schizophrenia (Jansen et al. 1998; Kaneda et al. 2002). Interestingly, previous studies indicate a relationship between HPA activity and symptomatology in schizophrenia. In some of them cortisol secretion was associated with more severe positive symptoms (Kaneko et al. 1992; Walder et al. 2000), whereas in others it was associated with higher ratings of negative symptoms (Newcomer et al. 1991; Tandon et al. 1991). Moreover, an association of DST non-suppression with negative symptoms in schizophrenia has been reported (Altamura et al. 1989; Newcomer et al. 1991; Tandon et al. 1991). These results suggest that HPA axis dysregulation/activation and hypercortisolemia are frequent abnormalities detected in a large proportion of schizophrenic patients and can influence drug response.

Cerebral atrophy and enlarged ventricles have been suggested as the structural changes underlying negative symptoms and poor response to neuroleptic treatment. Furthermore, a higher percentage of non-suppressors to the DST and of ventricular enlargement among negative schizophrenics has been described (Mauri et al. 1994).

Recently, it has been shown that HPA axis activation is elicited by exogenous cytokines, such as IL-1 or IL-6, when administered to rodents (Wang and Dunn 1999): on the other hand, several cytokines are also known to affect the release of anterior pituitary hormones by an action on the hypothalamus and/or the pituitary glands (Bumiller et al. 1999).

With respect to treatment response, few studies were performed with the aim to identify a relationship between antipsychotic response and immune system in schizophrenic patients. Maes et al. (2002) examined whether treatment-resistant schizophrenia is accompanied by some immune alterations and the effects of atypical antipsychotics on the above immune variables. Prolonged treatment with atypical antipsychotics may increase the anti-inflammatory capacity of the serum in schizophrenic patients by increasing serum leukaemia inhibitory factor receptor (LIF-R) concentrations, and short-term treatment with clozapine may induce signs of immune activation which disappear in the long-term treatment.

Lin et al. (1998) examined serum CC16 in relation to IL-6, IL-6R and gp130 (the IL-6 transducing signal protein) in schizophrenia and in treatment-resistant schizophrenia. Serum IL-6 and IL-6R were significantly higher in medicated schizophrenic patients than in normal controls. Serum IL-6 was significantly higher in resistant schizophrenia than in normal volunteers, whereas schizophrenic patients without drug resistance showed intermediate values. There was a significant inverse relationship between serum CC16 and serum IL-6 or IL-6R in schizophrenic patients but not in normal controls. These results suggest that inflammatory response in schizophrenia may be causally related to lower serum CC16 and that the latter may be a trait marker for schizophrenia.

In another study Maes et al. (2000) found that serum IL-6 was significantly higher in schizophrenic patients, irrespective of their response to neuroleptics. Moreover the serum concentration of CC16 was found to be significantly lower after 4 months treatment with atypical antipsychotics. These data suggest that schizophrenia, and in particular treatment-resistant schizophrenia, is characterized by an activation of the monocytic arm of cell-mediated immunity, and that atypical compounds may decrease the anti-inflammatory capacity of the serum in resistant patients.

Pharmacogenetics

Molecular genetic approaches provide a novel method of dissecting the heterogeneity of psychotropic drug response. These pharmacogenetic strategies offer the prospect of identifying biological predictors of psychotropic drug response and could provide the means of determining the molecular substrates of drug efficacy and drug-induced adverse events (Malhotra et al. 2004). The pharmacokinetics of antipsychotics has been focused mainly on the association between genetic polymorphisms in CYP genes, including CYP2D6, and the metabolism of these drugs. No relationship between CYP2D6 genotype or activity and therapeutic effects of 'classical' antipsychotic drugs has been found in the few studies performed. For the newer antipsychotics, such data are lacking. To date, CYP2D6 phenotyping and genotyping appear, therefore, to be clinically useful for dose predicting only in special cases and for a limited number of antipsychotics, while their usefulness in predicting clinical effects must be further explored (Scordo and Spina 2002).

Genetic variation in clozapine's receptor targets is a potential source of pharmacodynamic influence on drug response, by altering drug action. Polymorphisms in two genes, for 5-HT2A and D3, have been implicated in several studies, even if there is general lack of large, powerful prospective studies using multiple measures of response. In a meta-analysis by Arranz et al. (1998), including 373 patients who responded to clozapine treatment, and 360 non-responder patients, an association between two 5-HT2A polymorphisms (102/TC and His452Tyr) and clozapine response has been found.

A recent study (Mundo et al. 2004) investigated the role of the chemokine MCP-1 in the pathogenesis of schizophrenia, and in the resistance to antipsychotic treatment. The aim of this case–control study was to investigate the potential role of MCP-1 gene (SCYA2) (A-2518G polymorphism) in conferring susceptibility to schizophrenia and to the resistance to antipsychotic treatment. The sample studied consisted of 191 DSM-IV schizophrenia or schizoaffective disorder (depressive subtype) patients and 161 matched healthy controls. No significant genotypic ($\chi^2 = 0.278$, df = 2, $P = 0.986$) or allelic ($\chi^2 = 0.021$, df = 1, $P = 0.884$) association was found between the A-2518G variant of the SCYA2 gene and the diagnosis. No differences in the age at onset of schizophrenia were found between the three genotype groups identified.

Significant genotypic association was found between the A-2518G variant of the SCYA2 and the resistance to antipsychotic treatment ($\chi^2 = 6.26$, df = 2, $P = 0.04$), with resistant patients more frequently carrying the G allele. The odds ratio associated to the presence of the G allele was 2.39 (95% C.I. = 1.14–4.98).

These data suggest that the A-2518G variant of the SCYA2 does not have a major role in the pathogenesis of schizophrenia, while it could be implicated in the resistance to antipsychotic treatment.

Neuroimaging

Functional neuroimaging techniques, including single photon emission computerised tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (FMRI), can provide a direct *in vivo* assessment of the expression and function of neuroreceptors, transporters, and enzymes. Molecular imaging and the application of these techniques may increase insight into relationship between central neuroreceptor occupancy, psychotropic drug blood levels and clinical effects, and in the future is likely to play a valuable role in the acceleration of drug development for schizophrenia and other CNS disorders (Laruelle and Abi-Dargham 2003).

It has been reported that the response to clozapine may be associated with prefrontal and temporal anatomy, as well as with prefrontal, basal ganglia and thalamic metabolism. Improvement in positive symptoms with clozapine was directly related to temporal-gray matter volume. Improvement in disorganization symptoms was inversely related to intracranial and hippocampal volume. Patients with high baseline dorsolateral–prefrontal volume and metabolic activity were more likely to experience improvement in negative symptoms (Molina et al. 2003).

PET has been used in several studies to explore the relationship between central neuroreceptor occupancy, psychotropic drug blood levels, clinical response and side effects (e.g., EPS and hyperprolactinemia) in antipsychotic treatment. In a double-blind study, 22 patients with first episode schizophrenia were randomly assigned to 1 or 2.5 mg/day of haloperidol. After 2 weeks of treatment, they underwent PET and D2 receptor occupancy, EPS and prolactin levels were measured. Patients who showed adequate responses continued the initial therapy, non-responders had their doses increased to 5 mg/day and evaluations were repeated at 4 weeks for all patients. The patients showed a range of D2 occupancy of 38–87%. The degree of receptor occupancy predicted clinical improvement, hyperprolactinemia, and EPS. The likelihood of clinical response, hyperproactinemia, and EPS increased significantly as D2 occupancy exceeded 65, 72 and 78%, respectively, suggesting that D2 occupancy is an important mediator of response and side effects in antipsychotic treatment (Kapur et al. 2000) and explaining many of the observed clinical differences between typical and atypical antipsychotics.

Conclusions

Firstly, the definition of drug resistance is quite complex for psychiatric disorders, and particularly for schizophrenia; actually, we lack sound criteria to define poor versus full response and remission (Andreasen et al. 2005).

In the case of drug resistance it is of paramount importance to discriminate between 'pseudo' and real drug-resistance. The former is due to clinical variables (incorrect diagnosis, concomitant organic disorders, type of symptoms, side effects, etc.) and pharmacological ones (inadequate dosage and/or insufficient duration of treatment, use of 'depressogenic' drugs, poor compliance, etc). Moreover pharmacokinetic variables, leading to poor bioavailability and metabolic abnormalities, can contribute to drug response interindividual variability (Altamura et al. 1990; Altamura 1992).

Concerning 'real' drug resistance, the findings of biological markers of treatment resistance in schizophrenia and related disorders have indicated that some neurochemical findings (in particular dysfunction of dopaminergic, serotonergic and glutamatergic brain pathways) have been associated with variability in drug response, including drug resistance for typical and atypical compounds (Van der Heijden et al. 2004).

Moreover, drug resistance seems likely to be associated to IRS and HPA axis dysregulation, which could in turn be influenced by treatment with neuroleptics or atypical antipsychotics (Altamura et al. 1999): accordingly, CK gene polymorphisms have been associated with lack of treatment response (e.g., MCP-1). Other genetic studies proposed some D3 and 5-HT2A polymorphisms in conferring susceptibility to resistance to antipsychotic treatment (Arranz et al. 1998).

In general, some of these aspects, e.g., neurochemical and psychoimmunological, can at least partially contribute to explain differences in the clinical response to typical and atypical antipsychotic compounds: as for instance in the case of the effect of atypical antipsychotics (in comparison to neuroleptics) on glutamatergic pathways, which can explain their specificity for symptoms, especially negative ones (Tascedda et al. 2001).

Finally, PET studies could contribute to a better understanding of the mechanisms of drug response to antipsychotics being possibly related to specific brain region volume abnormalities (Laruelle and Abi-Dargham 2003; Molina et al. 2003). All these data do not allow us to be overoptimistic in the short term, but encourage us to continue to improve in our understanding of these important biological aspects which determine drug response in schizophrenia.

In conclusion, a multidimensional approach, taking into account all these variables in the near future, would likely be the more valuable strategy to optimize response, reducing relapses or frankly refractory clinical situations. Thus an 'ideal' treatment for schizophrenia could be tailored for a patient on the basis of his individual biological 'profile': a more rational treatment would therefore be implemented with relevant impact on patient suffering and social costs.

Statement of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

References

Altamura AC. 1990. Drug-resistance phenomena in major psychoses: their discrimination and causal mechanisms. Clin Neuropharmacol 13:s1–15.

Altamura AC. 1992. A multidimensional (pharmacokinetic and clinical-biological) approach to neuroleptic response in schizophrenia. With particular reference to drug resistance. Schizophr Res 8:187–192.

Altamura AC, Guercetti G, Percudani M. 1989. Dexamethasone suppression test in positive and negative schizophrenia. Psychiatr Res 30:69–75.

Altamura AC, Boin F, Maes M. 1999. HPA axis and cytokines dysregulation in schizophrenia: potential implications for the antipsychotic treatment. Eur Neuropsychopharmacol 10:1–4.

Altamura AC, Velonà I, Curreli R, Mundo E, Bravi D. 2002. Is olanzapine better than haloperidol in resistant schizophrenia? A double-blind study in partial responders. Int J Psychiatr Clin Pract 6:107–111.

American Psychiatric Association. 1997. Practice guidelines for the treatment of patients with schizophrenia. Am J Psychiatry 154(Suppl):1–63.

Andreasen NC, Olsen S. 1982. Negative vs positive schizophrenia. Definition and validation. Arch Gen Psychiatry 39(7): 789–794.

Andreasen N, Carpenter W, Kane JM, Lasser RA, Marder SR, Weinberger DR. 2005. Remission in schizophrenia: Proposed criteria and rationale for consensus. Am J Psychiatry 162:41–49.

Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P. 1995. A longitudinal study of symptom dimensions in schizophrenia. Prediction and patterns of change. Arch Gen Psychiatry 52(5):352–360.

Arolt V, Rothermundt M, Wandinger KP, Kirchner H. 2000. Decreased in vitro production of interferon-gamma and interleukin-2 in whole blood of patients with schizophrenia during treatment. Mol Psychiatry 5:150–158.

Arranz Mj, Munro J, Sham P. 1998. Meta analysis of studies on variation in 5HT2A receptors and clozapine response. Schizophr Res 32:93–99.

Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK. 1985. Symptomatic and neuropsychological components of defect states. Schizophr Bull 11:409–419.

Boin F, Zanardini R, Pioli R, Altamura AC, Maes M, Gennarelli M. 2001. Association between –G308A tumor necrosis factor alpha gene polymorphism and schizophrenia. Mol Psychiatry 6(1):79–82.

Bowers MB, Swigar ME, Jatlow PI, Goicoechea N. 1984. Plasma catecholamine metabolites and early response to haloperidol. J Clin Psychiatry 45:248–251.

Breier A, Buchanam RW, Kirkpatrick B, Davis OR, Irish D, Sommerfelt A, Carpenter NT. 1994. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 181:20–26.

Bumiller A, Gotz F, Rohde W, Dorner G. 1999. Effects of repeated injections of interleukin 1beta or lipopolysaccharide on the HPA axis in the newborn rat. Cytokine 11:225–230.

Chengappa KN, Ganguli R, Yang ZW, Shurin G, Brar JS, Rabin BS. 1995. Impaired mitogen (PHA) responsiveness and increased autoantibodies in Caucasian schizophrenic patients with the HLA B8/DR3 phenotype. Biol Psychiatry 37:546–549.

Coryell W, Tsuang D. 1992. Hypothalamic-pituitary-adrenal axis hyperactivity and psychosis: recovery during an 8-year follow-up. Am J Psychiatry 149:1033–1039.

Doyle AC, Pollack MH. 2003. Establishment of remission criteria for anxiety disorders. J Clin Psychiatry 64(Suppl 15):40–45.

Emsley RA, Raniwilla J, Bailey PJ, Jones AM. 2000. A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol 15(3):121–131.

Ganguli R, Yang Z, Shurin G, Chengappa RKN, Brar JS, Gubbi AV, Rabin BS. 1994. Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness. Psychiat Res 51:1–10.

Ganguli R, Brar JS, Chengappa KNR, Deleo M, Yang ZW, Shurin G. 1995. Mitogen-stimulated interleukin-2 production in

never-medicated, first-episode schizophrenic patients. Arch Gen Psychiatry 52:668–672.

Garver DL, Holcomb JA, Christensen JD. 2000. Heterogeneity of response to antipsychotics from multiple disorders in the schizophrenia spectrum. J Clin Psychiatry 61:964–972.

Henneberg AE, Horter S, Ruffert S. 1994. Increased prevalence of antibrain antibodies in the sera from schizophrenic patients. Schizophr Res 14:15–22.

Jansen LM, Gispen-de Wied CC, Gademan PJ, De Jonge RC, van der Linden JA, Kahn RS. 1998. Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr Res 33:87–94.

Kahn RS, Davidson M, Knott P, Stern RG, Apter S, Davis KL. 1993. Effect of neuroleptic medication on cerebrospinal fluid monoamine metabolites concentrations in schizophrenia. Arch Gen Psychiatry 50:599–605.

Kane JM, Honigfeld G, Singer J, Meltzer H. 1988. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796.

Kaneda Y, Fujii A, Ohmori T. 2002. The hypothalamic–pituitary–adrenal axis in chronic schizophrenic patients long-term treated with neuroleptics. Prog Neuropsychopharmacol Biol Psychiatry 26:935–938.

Kaneko M, Yokoyama F, Hoshino Y, Takahagi K, Murata S, Watanabe M, Kumashiro H. 1992. Hypothalamic-pituitary-adrenal axis function in chronic schizophrenia: association with clinical features. Neuropsychobiology 25:1–7.

Kapur S, Zipursky R, Jones C, Remington G, Houle S. 2000. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 157(4):514–520.

Kim YK, Kim L, Lee MS. 2000. Relationship between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. Schizophr Res 44:165–175.

Lammers CH, Garcia-Borreguero D, Schmider J, Gotthardt U, Dettling M, Holsboer F, Heuser IJ. 1995. Combined dexamethasone/corticotropin-releasing hormone test in patients with schizophrenia and in normal controls. Biol Psychiatry 38:803–807.

Laruelle M, Abi-Dargham A. 2003. Imaging drug action in schzophrenia: Research update. Eur Psychiatry 18:32–37s.

Licinio J, Seibyl JP, Altemus M, Charney DS, Krystal JH. 1993. Elevated CSF levels of interleukin-2 in neuroleptic-free schizophrenic patients. Am J Psychiatry 150:1408–1410.

Liddle PF, Friston KJ, Frith CD, Frackowiak RSJ. 1992. Cerebral blood flow and mental processes in schizophrenia. J Royal Soc Med 85(4):224–226.

Lieberman JA, Kane JM, Safferman AZ, Pollack S, Howard A, Szymanski S, Masiar SJ, Kronig MH, Cooper T, Novacenko H. 1994. Predictors of response to clozapine. J Clin Psychiatry 55:126–128.

Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, Gilmore J. 2001. The early stages of schizophrenia: Speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry 50:884–897.

Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, Pioli R, Altamura AC, Scharpe S, Maes M. 1998. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res 32(1):9–15.

Maes M, Bosmans E, Calabrese J, Smith R, Meltzer H. 1995. Interleukin-2 and interleukin-6 in schizophrenia and mania: Effects of neuroleptics and mood stabilizers. J Psychiatr Res 29:141–152.

Maes M, Bosmans E, Kenis G, DeJong R, Smith RS, Meltzer HY. 1997. In vivo immunomodulatory effects of clozapine in schizophrenia. Schizophr Res 26:221–225.

Maes M, Bocchio Chiavetto L, Bignotti S, Tura G, Pioli R, Boin F, Kenis G, Bosmans E, De Jong R, Lin A, Racagni G, Altamura AC. 2000. Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. Eur Neuropsychopharmacol 10(2):119–124.

Maes M, Bocchio Chiavetto L, Bignotti S, Tura G, Pioli R, Boin F, Kenis G, Bosmans E, De Jongh R, Altamura AC. 2002. Increased serum interleukin-8 and interleukin-10 in schizophrenic patients resistant to treatment with neuroleptics and the stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. Schizophr Res 54:281–291.

Malhotra AK, Murphy GM Jr, Kennedy JL. 2004. Pharmacogenetics of psychotropic drug response. Am J Psychiatry 161(5):780–796.

Marx CE, Lieberman JA. 1998. Psychoneuroendocrinology of schizophrenia. Psychiatr Clin North Am 21:413–434.

Mauri MC, Vita A, Giobbio GM, Ferrara A, Dieci M, Bitetto A, Altamura AC. 1994. Prediction of response to haloperidol in schizophrenia: Neuroendocrine, neuromorphological and clinical variables. Int Clin Psychopharmacol 9(1):3–7.

Mazure CM, Nelson JC, Jatlow PI, Bowers MB. 1991. Plasma free homovanillic acid (HVA) as a predictor of clinical response in acute psychosis. Biol Psychiatry 30:475–482.

Molina V, Reig S, Sarramea F, Sanz J, Francisco Artaloytia J, Luque R, Aragues M, Pascau J, Benito C, Palomo T, Desco M. 2003. Anatomical and functional brain variables associated with clozapine response in treatment-resistant schizophrenia. Psychiatry Res 124(3):153–161.

Mundo E, Altamura AC, Vismara S, Zanardini R, Bignotti S, Randazzo R, Montresor C, Gennarelli M. 2004. MCP-1 gene (SCYA2) and schizophrenia: a case-control study. Am Med Genet 132B(1):1–4.

Muller N, Hofschuster E, Ackenheil M, Eckstein R. 1993. T-cells and psychopathology in schizophrenia: Relationship to the outcome of neuroleptic therapy. Acta Psychiatr Scand 87:66–71.

Newcomer JW, Faustman WO, Witheford HA, Moses JA Jr, Csernansky JG. 1991. Symptomatology and cognitive impairment associate independently with post-dexamethasone cortisol concentrations in unmedicated schizophrenic patients. Biol Psychiatry 29:855–864.

Pantelis C, Lambert T Jr.. 2003. Managing patients with 'treatment-resistant' schizophrenia. Med J Aust 178(9):62–66.

Rapaport MH, McAllister CG, Kim YS, Han JH, Pickar D, Nelson DL, Kirch DG, Paul SM. 1994. Increased serum soluble interleukin-2 receptors in Caucasian and Korean schizophrenic patients. Biol Psychiatry 35:767–771.

Rapaport MH, McAllister CG, Pickar D, Tamarkin L, Kirch DG, Paul SM. 1997. CSF IL-1 and IL-2 in medicated schizophrenic patients and normal volunteers. Schizophr Res 25:123–129.

Scheepers FE, Gispen-de Wied CG, Westenberg HGM, Kahn RS. 2001. The effect of olanzapine treatment on monoamine metabolite concentrations in the cerebrospinal fluid of schizophrenic patients. Neuropsychopharmacology 25(4):468–475.

Scordo MG, Spina E. 2002. Cytochrome P450 polymorphisms and response to antipsychotic therapy. Pharmacogenetics 3(2):201–218.

Sharma RP, Pandey GN, Janicak PG, Peterson J, Comaty JE, Davis JM. 1988. The effect of diagnosis and age on the DST: a metaanalytic approach. Biol Psychiatry 24:555–568.

Sheitman BB, Lieberman JA. 1998. The natural history and pathophysiology of treatment resistant schizophrenia. J Psychiatr Res 32(3–4):143–150.

Szymanski S, Lieberman J, Pollack S, Munne R, Safferman A, Kane J, Kronig M, Cooper T. 1993. The dopamine-serotonin

relationship in clozapine response. Psychopharmacology 112(1 Suppl):S85–89.

Tandon R, Mazzara C, DeQuardo J, Craig KA, Meador-Woodruff JH, Goldman R, Greden JF. 1991. Dexamethasone suppression test in schizophrenia: relationship to symptomatology, ventricular enlargement, and outcome. Biol Psychiatry 29:953–964.

Tascedda F, Lovati E, Blom JM, Muzzioli P, Brunello N, Racagni G, Riva MA. 1999. Regulation of ionotropic glutamate receptors in the rat brain in response to the atypical antipsychotic Seroquel (quetiapine fumarate). Neuropsychopharmacology 21(2):211–217.

Tascedda F, Blom JM, Brunello N, Zolin K, Gennarelli M, Colzi A, Bravi D, Carra S, Racagni G, Riva MA. 2001. Modulation of glutamate receptors in response to the novel antipsychotic olanzapine in rats. Biol Psychiatry 50(2):117–122.

Van der Heijden FMMA, Tuinier S, Fekkes D, Sijben AES, Kahn RS, Verhoeven WMA. 2004. Atypical antipsychotics and the relevance of glutamate and serotonin. Eur Neuropsychopharmacol 14:259–265.

Walder DJ, Walker EF, Lewine RJ. 2000. Cognitive functioning, cortisol release, and symptom severity in patients with schizophrenia. Biol Psychiatry 48:1121–1132.

Walker EF, Diforio D. 1997. Schizophrenia: A neural diathesis-stress model. Psychol Rev 104:667–685.

Wang J, Dunn AJ. 1999. The role of interleukin-6 in the activation of the hypothalamo-pituitary-adrenocortical axis and brain indoleamines by endotoxin and interleukin-1 beta. Brain Res 815:337–348.

Wieselgren IM, Lindstrom LH. 1998. CSF levels of HVA and 5-HIAA in drug-free schizophrenic patients and healthy controls: a prospective study focused on their predictive value for outcome in schizophrenia. Psychiatr Res 81:101–110.

Yeragani VK. 1990. The incidence of abnormal dexamethasone suppression in schizophrenia: A review and a meta-analytic comparison with the incidence in normal controls. Can J Psychiatry 35:128–132.

Yoshimura R, Ueda N, Shinkai K, Nakamura J. 2003. Plasma levels of homovanillic acid and the response to risperidone in first episode untreated acute schizophrenia. Int Clin Psychopharmacol 18(2):107–111.

Zhang XY, Zhou DF, Zhang PY, Wu GY, Shen YC. 2002a. Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophr Res 57:247–258.

Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY. 2002b. Decreased production of interleukin-2 (IL-2), IL-2 secreting cells and CD4+ cells in medication-free patients with schizophrenia. J Psychiatr Res 36:331–336.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 31–37

LECTURE

Depressive subtypes and efficacy of antidepressive pharmacotherapy

JOSÉ L. AYUSO-GUTIÉRREZ

Universidad Complutense, Madrid, Spain

Abstract
Efficacy studies suggest that all kinds of treatment have similar efficacy. For instance, according to a meta-analysis from 102 randomised controlled trials in major depression, there is no overall difference in efficacy between SSRIs and TCAs. Taking into consideration the pathophysiological heterogeneity of affective disorders involving a number of neurotransmitters, the different pharmacodynamic profiles of the antidepressant compounds, and the large variety of presentations of depressive illness, it is very simplistic to suppose that all classes of antidepressants are equally effective. Meanwhile, the development of antidepressants with different mechanisms of action provides the opportunity to evaluate whether certain relevant subtypes of depressed patients, based on specific patterns of symptoms, respond preferentially to one class of antidepressants compared with another. The aim of this paper is to review the relationship between the depressive subtypes included in the DSM-IV (melancholic depression, atypical depression, bipolar depression, psychotic bipolar and dysthymia) and the efficacy of antidepressant treatment.

Key words: *Efficacy, antidepressants, melancholia, atypical depression, bipolar depression*

Introduction

Successful antidepressant treatment is one of the most effective ways to reduce disability, prevent morbidity, and improve quality of life in depressed patients. Since Roland Kuhn introduced imipramine and Nathan Kline iproniazid in the 1950s, the availability of antidepressant compounds has expanded greatly, not only in terms of number but also in terms of diversity of pharmacological effects. In the late 1980s, the introduction of new antidepressants, with different mechanisms of action, has had a revolutionary impact on the treatment of depressive illness. This group comprise selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, reversible monoamine oxidase inhibitors, 5-HT2 antagonists, α_2-antagonists and noradrenaline reuptake inhibitors. Moreover, in the not-so-distant future we will also have new compounds developed, based on other mechanisms of action that extend beyond the monoamines, which offer promising perspectives as melatonin receptor agonists and corticotropin-releasing factor antagonists.

When treating depressive patients we have to decide which antidepressant to prescribe. However, despite the wide range of compounds with different pharmacodynamic profiles, efficacy studies suggest that all kinds of treatment have similar efficacy. For instance, according to a meta-analysis (Anderson 2000) from 102 randomised controlled trials in major depression patients, there is no overall difference in efficacy between SSRIs and TCAs. Moreover, after 16 weeks of treatment, aerobic exercise was equally effective as sertraline in reducing depression among patients with major depression disorder (Blumenthal et al. 1999), and a comparison of St John's wort (*Hypericum perforatum*) to imipramine in a randomised controlled trial shows that both treatments are therapeutically equivalent in treating mild to moderate depression (Woelk 2000). How can this amazing fact be explained? Taking into consideration the pathophysiological heterogeneity of affective disorders involving a number of neurotransmitters (NA, 5-HT, acetylcholine, dopamine, GABA, CRH, CCK), the different pharmacodynamic profiles of the antidepressant compounds, and the large variety of presentations of depressive illness, it is very simplistic to suppose that all classes of antidepressants are equally effective.

Meanwhile, the development of antidepressants with different mechanisms of action provides the

Correspondence: José L. Ayuso-Gutiérrez, Department of Psychiatry, Universidad Complutense, Alcalá 152, Madrid 28028, Spain. E-mail: jlayusogut@teleline.es

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030036

opportunity to evaluate whether certain relevant subtypes of depressed patients based on specific patterns of symptoms respond preferentially to one class of antidepressants compared with another. The aim of this paper is to review the relationship between the depressive subtypes included in the DSM-IV (melancholic depression, atypical depression, bipolar depression, psychotic bipolar and dysthymia) and the efficacy of antidepressant treatment.

Melancholic depression

Which antidepressant compound is more effective in melancholic depression?

The available evidence demonstrates less efficacy of SSRIs in melancholic depressed patients compared with the conventional heterocyclics. In one trial carried out by the Danish University Antidepressants Group (1986), with 114 patients with endogenous depression, the rates of positive response obtained with clomipramine (150 mg/day) were significantly superior to those reached by citalopram (40 mg/day). After 5 weeks of treatment, clinical remission (HAMD17 <7) was more likely in clomipramine-treated patients (62%) than in citalopram-treated patients (34%). The same research team (DUAG 1990) carried out another comparative study between paroxetine and clomipramine. Using identical protocol as in the initial study, 120 inpatients were randomized to either a fixed dose of clomipramine (150 mg/day) or paroxetine (30 mg/day) for 6 weeks. A complete remission (HAMD17 <7) was more likely in clomipramine-treated patients (56%) than in the paroxetine group (25%).

Tignol et al. (1992) performed a meta-analysis of the manufacturer's database involving paroxetine treatment of melacholic depressions. The analysis included 178 patients treated with paroxetine and 66 patients treated with placebo. The paroxetine response data were remarkable consistent with the two DUAG studies. Only 31% of the paroxetine patients and 15% of the placebo had a final HAMD score of -10.

Roose et al. (1994) retrospectively contrasted the treatment responses of the TCA nortrtiptyline (1 mg/kg per day) and fluoxetine (20–60 mg/day) in a group of 45 depressed melancholic geriatric inpatients treated for 7 weeks. As in the previous studies, the findings favoured the TCA over the SSRI: 63% of the nortriptyline group and only 8% of the fluoxetine group had a final HAMD score of -8.

Among the new antidepressant compounds, venlafaxine has received much of the attention in the treatment of melancholic patients. Three double-blind studies support the superiority of venlafaxine over fluoxetine. Clerc et al. (1994) randomized 67 melancholic inpatients to either venlafaxine (200 mg/day) or fluoxetine (40 mg/day). A response, defined as a 50% decrease in HAMD total score, was found in 73% of patients treated with venlafaxine versus a 50% response rate for patients in the fluoxetine group. Thase et al. (2001) reported a response rate (HAMD <7) of 55% for venlafaxine and only 26% for fluoxetine, and Tzanakaki (2000) conducted a controlled trial in which venafaxine (225 mg/day) was compared to fluoxetine (60 mg/day) in 93 melancholic inpatients, finding that a CGI improvement score of 1 was observed in 51% of patients with venlafaxine and 32% with fluoxetine. On the other hand, Benkert (1996) has demonstrated that venlafaxine has equal efficacy to imipramine in a 6-week multicentre study with melancholic patients.

Regarding milnacipran, an antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake, Von Frenckell et al. (1990) compared this compound (200 mg/day) with amitriptyline (150 mg/day) in randomized groups of major depressive inpatients with endogenous depression, and found similar improvement with both drugs after 4 weeks of treatment.

The antidepressant efficacy of mirtazapine, an α_2-antagonist, in melancholic patients was assessed by Guelfi et al. (2001) in a multicentre, double-blind, 8-week study, comparing the antidepressant action of mirtazapine (15–60 mg/day) with venlafaxine (75–375 mg/day). No statistically significant differences, at all assessment times, were found among both medications.

There is a lack of information on the efficacy, in melancholia, of duloxetine, another inhibitor of noradrenaline and serotonin uptake, and reboxetine, a selective inhibitor of noradrenaline uptake.

Regarding electroconvulsive therapy, melancholic features are a predictor of a good response (Carney and Sheffield 1972; Abou-Saleh and Coppen 1983; Parker et al. 2001).

With respect to psychotherapy, Thase and Friedman (1999) have reviewed the available research on the treatment of melancholia with psychotherapy, e.g., cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT), concluding that, although some melancholic patients are responsive to IPT or CBT, there is not as yet compelling evidence that melancholic patients respond to psychotherapy as well as they do to medications

In summary, taking together all data, tricyclic antidepressants are more effective than SSRI, and new dual-action antidepressants are also more effective than SSRI in the treatment of major depression

with melancholic features. ECT is also an alternative treatment for melancholic depression.

Atypical depression

Atypical depression, has been included in the DSM-IV as an episode specifier of major depressive episodes and dysthymia, that has high population prevalence. The disorder is primarily characterized by two or more of the following symptoms: overeating, oversleeping, 'leaden paralysis', and sensitivity to interpersonal rejection.

There are supporting data for the diagnostic validity of atypical depression in the criteria of clinical description and differential treatment response, with atypical depression having a superior response to monoamine oxidase (MAO) inhibitors compared to tricyclic antidepressants. The evidence on the superiority of phenelzine, an MAO inhibitor, appears to be overwhelming. Data from six trials, performed by investigators from Columbia University (Quitkin et al. 1993), all showed phenelzine to be significantly superior to imipramine. These data, which included results from 269 patients, show that 72% of patients responded to phenelzine, whereas the response rate in the imipramine group was 44%, supporting that the presence of associated atypical features confers selective responsivity to MAOI therapy.

Moclobemide, a reversible inhibitor of monoamine oxidase type A, has also be used in atypical depression, but its efficacy has not been sufficiently established. Two double-blind controlled studies comparing moclobemide and diazepam in atypical depression (Schweitzer et al. 1989; Tiller et al. 1989) found that significant decreases in depression ratings occurred in both groups, but there was no significant difference between the two drugs in depression scores. On the other hand, two comparisons of moclobemide with sertraline in depressives with atypical features offer different results: while Lonnqvist et al. (1994) found significant differences in MADRS and GCI scores in favour of moclobemide, in another trial Sogaard et al. (1999) found that mean changes from baseline to last visit for HAMD and Clinical Global Impression were greater for sertraline than moclobemide. In other comparison (Larsen et al. 1991), moclobemide (300 mg/day) was less effective at 6-week end-point than either isocarboxacide (30 mg/day) and clomipramine (150 mg/day).

In despite of earlier data that SSRIs might be the treatment of choice, fluoxetine in a placebo-controlled comparison with imipramine (McGrath et al. 2000) appears to be no better. Both treatments were significantly superior than placebo, but the two medications did not differ from each other in effectiveness. However, in a 6-week, double-blind study (Pande et al. 1996), that compared the relative efficacy of fluoxetine and phenelzine in 42 patients with atypical depression, the rates of treatment response did not differ between groups.

Davidson et al. (2003) have reported that chromium picolinate benefits patients with symptoms of atypical depression. In a placebo-controlled, 8-week pilot study with 15 patients with DSM-IV major depressive disorder, atypical type, seven (70%) patients receiving chromium (600 μg/day) and no (0%) of patients on placebo met responder criteria ($P=0.02$).These preliminary results need further research to assess its utility in the treatment of atypical depression.

Unfortunately, there is a lack of studies comparing MAOIs to the new generation of antidepressants, including the dual action compounds (venlafaxine, milnacipran, mirtazapine).

Regarding psychotherapy, Jarrett et al. (1999) have performed a 10-week, double-blind, controlled trial, comparing cognitive therapy or clinical management plus either phenelzine sulfate or placebo in 108 outpatients with major depressive disorder and atypical features. The response rates (21-item HRSD score ≤ 9) were significantly greater after cognitive therapy (58%) and phenelzine (58%) than after placebo (28%). Therefore, cognitive therapy may offer an effective alternative to drug treatment.

In summary, there is good response to non-selective MAOIs and lower response to tricyclics. The efficacy of SSRIs appears to be at least similar to tricyclics and the efficacy of moclobemide is not well established. There is a lack of studies with the new generation of antidepressants. The most prudent approach appears to be using SSRIs as first-line treatment for atypical depression and reserving MAOIs for patients who do not respond. Cognitive therapy may offer an effective therapeutic alternative.

Bipolar depression

Antidepressants have different effects in bipolar patients, therefore the treatment of bipolar depression, the predominant mood state in bipolar illness, poses unique challenges for clinicians.

According to several guidelines, the first-line pharmacological treatment for bipolar depression is the initiation of a mood stabilizer. In patients who, despite receiving maintenance treatment suffer a depressive episode, the first-line intervention should be to maximize the dose of the maintenance medication. Antidepressives are recommended only as a second-line treatment and always with a con-

current mood stabilizer to prevent switching to mania. Among the different mood stabilizers, the antidepressant efficacy of lithium is well established (Goodwin et al. 1972; Fieve et al. 1968) its effect being associated with serum levels (Nemeroff et al. 2001). The antidepressant efficacy of lamotrigine has been demonstrated by Calabrese et al. (1999) in a multicentre placebo-controlled trial. With lamotrigine (200 mg/day) in monotherapy, the response rate (51%) was significantly higher than with placebo (26%). The therapeutic effect in bipolar depressive episodes of carbamazepine and valproate are not sufficiently documented. The efficacy of other mood stabilizers needs to be addressed in randomized controlled studies.

Antidepressants are indicated in depressive episodes that persist, despite optimization of mood stabilizers, or in episodes that are markedly severe.

Do antidepressants work in acute bipolar depression as well as they do in unipolar depression? According to a large comparative study (Geddes et al. 2003), antidepressants may be of comparable efficacy in unipolar and bipolar depression.

Are some antidepressants more effective than others in bipolar depression? The existing evidence does not support any substantial difference in efficacy among a number of compounds. In a review of six trials (Gijsman et al. 2004), tricyclic antidepressants may be less effective (response rate) than other antidepressants, but this did not reach statistical significance. On the other hand, according to a 10-week, placebo-controlled trial, there is no difference in remission rates between imipramine and paroxetine (Nemeroff et al. 2001).

Long-term use of antidepressant drugs may adversely affect the course of bipolar illness (switch into mania or hypomania, induction of a rapid cycling course). According to a naturalistic study (Post 2001), the rate of switch in bipolar patients treated with antidepressants of different classes is 18% at 10 weeks and 35% at 1-year follow-up. However, this risk is not similar with all antidepressants, being higher with tricyclics than with SSRIs (Peet 1994), with venlafaxine than with paroxetine (Vieta et al. 2002) and with desipramine than bupropion (Sachs et al. 1994).

Atypical antipsychotics are promising drugs, but efficacy in bipolar depression is not yet sufficiently documented.

ECT should be considered for patients with treatment-resistant depressive episodes and for patients with high risk of suicide and with psychotic features.

In summary, mood stabilizers are the cornerstone of therapy and antidepressants should be used with caution. SSRIs present less risk of inducing mania than tricyclics and the new dual-action antidepressants.

Psychotic depression

Psychotic depression, evidenced by depressed mood, profound psychomotor disturbance and psychotic features (mainly delusions but occasionally hallucinations) is a striking example of a treatment differential effect for a particular depressive disorder. These patients have the highest levels of serum cortisol and greatest resistance to its suppression with exogenous steroids as measured in dexamethasone suppression tests (Rothschild et al. 1993). Such abnormal neuroendocrine functions, and the differential response rates to antidepressant drugs, encouraged many investigators to the view that psychotic depression is a unique psychopathologic entity.

When the TCAs were introduced for the treatment of depression, reports began to appear that they were not as effective for psychotic depression as in non-psychotic depressed patients (Friedman et al. 1961). A literature review (Chan et al. 1987) of 1054 patients revealed that 67% of the nonpsychotic depressed patients ($N=691$) responded to TCAs compared with only 35% of the psychotic depressed patients ($N=363$).

In fact, it is strongly recommended (*Guidelines for Biological Treatment of Unipolar Depressive Disorders, WFSBP*, Bauer et al. 2003) that psychotic depression should be treated pharmacologically using a neuroleptic combined with an antidepressant. This recommendation is based on the evidence of the superior efficacy of the combined treatment. In a large double-blind trial assigning patients on a random basis to amitriptyline alone, perphenazine alone, or amitriptyline plus perphenazine, the combination was the superior treatment with a response rate of 78% compared with 41% for amitriptyline alone and 19% for perphenazine alone (Spiker et al. 1985).

Although there have been no prospective studies comparing TCAs and SSRIs (combined with an antipsychotic) for the treatment of psychotic depression, several trials suggest that SSRIs combined with an antipsychotic are an effective treatment for acute episodes of psychotic depression (Wolfersdorf et al. 1995). Unfortunately, there is a lack of information regarding the new generation of antidepressants.

Atypical antipsychotic medications may have particular relevance for psychotic depressive treatment because of their better side-effect profile and their effects on serotonin type-2 receptors. Several case and retrospective reports (Keck et al. 1995; Rothschild et al. 1999; Zarate et al. 2000), and a double-

blind, randomized study of olanzapine versus olanzapine/fluoxetine combination (Rothschild et al. 2004), suggest that atypical antipsychotics may be at least as effective as the conventional neuroleptics in patients with psychotic depression.

The efficay of ECT in the treatment of psychotic depression is well documented (Petrides et al. 2001; Birkenhäger et al. 2003). The outcome of an acute bilateral ECT course in 253 patients with nonpsychotic and psychotic unipolar major depression was assessed by Petrides et al. (2001), demonstrating that, among the patients with psychotic depression, the remission rate was higher (95%) than in nonpsychotic depressed patients (83%).

Finally, a promising alternative is the anti-glucocorticoid strategy. As mentioned above, patients with psychotic depression exhibit a marked dysregulation of the HPA axis in the acute episode. In longitudinal studies, many patients continue to exhibit elevated cortisol levels despite symptomatic improvement. Based on these observations, the steroid mifepristone, which is an effective antagonist of glucocorticosteroid action *in vitro* and *in vivo*, has been proposed as a new treatment of dysthymia. Belanoff et al. (2001) have reported on five patients who participated in a 4-day, double-blind, placebo-controlled, crossover study using 600 mg of mifepristone as monotherapy. All five patients showed substantial improvement in their HDRS scores, with little improvement with placebo.

In summary, the best options are combined treatment (antidepressant + antipsychotic) and E.C.T.

Dysthymia

Dysthymic disorder is a prevalent form of chronic subthreshold depressive disorder, associated with considerable disability and high comorbidity. Since these patients were previously labelled either as 'neurotic depression' or 'depressive personality', dysthymia was considered to be non-responsive to antidepressant treatment, and the interest necessary for controlled studies was not stimulated. In the last two decades, after the definition of the disorder in DSM-III, there has been a renewed interest in the research and treatment of dysthymia, although the literature is still limited. Nevertheless, dysthymia is a controversial and heterogeneous entity (pure dysthymia versus double depression; primary versus secundary dysthymia; comorbid versus non-comorbid personality disorder). This heterogeneity may explain why roughly one-half of dysthymic patients do not respond to antidepressant medication, while a substantial percentage of patients may respond to psychotherapy (Ravindran et al. 1999).

Placebo-controlled studies on the treatment of dysthymia with antidepressants have been few, particularly in samples without concurrent major depression, and most of them were of short duration. All comparisons with placebo show superior efficacy of the active compound: imipramine (Kocsis et al. 1988), desipramine (Miller et al. 2001), phenelzine (Stewart et al. 1988), moclobemide (Versiani et al. 1997), fluoxetine (Hellerstein et al. 1993; Vanelle et al. 1997), sertraline (Ravindran et al. 2000) and paroxetine (Katon et al. 2002). These results provide substantial evidence for the efficacy of antidepressants in dysthymia, although the treatment response is less than that typically found in major depression.

In addition to antidepressants, the pharmacological treatment of dysthymia has also used amisulpride, a selective antagonist for D2 and D3 dopamine receptors that acts preferentially on presynaptic receptors increasing dopaminergic transmission at low doses. Three large double-blind studies, comparing amisulpride with sertraline for 12 weeks (Amore and Jori 2001), amitriptyline for 6 months (Ravizza 1999) and amineptine for 3 months (Boyer et al. 1999), show that both drugs were equally effective at end-point.

Is any drug more effective in the treatment of dysthymic disorder? The answer is clearly negative. According to a meta-analysis (Lima and Hotopf 2003) based on 25 trials, similar results were obtained in terms of efficacy for different groups of drugs, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other drugs (sulpiride, amineptine, and ritanserin).

The limitations of antidepressant medication argue for the development of effective psychotherapeutic interventions. Although long-term psychodynamic therapy is frequently prescribed, there is no evidence that psychodynamic treatment benefits such patients. On the other hand, cognitive approaches have been frequently applied in dysthymic patients. Markowitz (1994) has reviewed seven uncontrolled studies of cognitive-behavioral treatment for dysthymia, finding that the cumulative response of 41% approaches the efficacy reported for antidepresants trials.

In summary, pharmacotherapy for disthymia appears to be an effective short-term treatment for dysthymic disorder with no diffrences between various types of drugs. Since there is not sufficient evidence for one group of drugs to be declared more effective than the other, the more tolerated antidepressant should generally be prescribed. Psychotherapy, specially behaviour therapy, is also effective.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Abou-Saleh MT, Coppen A. 1983. Classification of depression and response to antidepressive therapies. Br J Psychiatry 143:601–603.

Amore M, Jori MCFaster. 2001. Response on amisulpride 50 mg versus sertraline 50–100 mg in patients with dysthymia or double depression: a randomized, double-blind, parallel group study. Int Clin Psychopharmacol 16(6):317–324.

Anderson M, Nutt D J, Deakin J F W. 2000. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology Guidelines. J Psychopharmacol 14:3–20.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ; World Federation of Societies Biological Psychiatry Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry. 2002. Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 3(1):5–43.

Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. 2001. Rapid reversal of psychotic depression using mifepristone. J Clin Psychopharmacol 21(5):516–521.

Benkert O, Grunder G, Wetzel H, Hackett D. 1996. A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res 30(6):441–451.

Birkenhäger TK, Pluijms EM, Lucius SA. 2003. ECT response in delusional versus non-delusional depressed inpatients. J Affect Disord 74(2):191–195.

Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P, Waugh R, Napolitano MA, Forman LM, Appelbaum M, Doraiswamy PM, Krishnan KR. 1999. Effects of exercise training on older patients with major depression. Arch Intern Med 25;159(19):2349–2356.

Boyer P, Lecrubier Y, Stalla-Bourdillon A, Fleurot O. 1999. Amisulpride versus amineptine and placebo for the treatment of dysthymia. Neuropsychobiology 39(1):25–32.

Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. 1999. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 60:79–88.

Carney MW, Sheffield BF. 1972. Depression and Newcastle scales.Their relationship to Hamilton's scale. Br J Psychiatry 121(560):35–40.

Chan CH, Janicak PG, Davis JM, Altman E, Andriukaitis S, Hedeker D. 1987. Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. J Clin Psychiatry 48(5):197–200.

Clerc GE, Ruimy P, Verdeau-Palles J. 1994. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 9:139–143.

Danish University Antidepressant Group. 1986. Citalopram: Clinical effect profile in comparison with clomipramine. A controlled multicenter study. Psychopharmacology 90:131–138.

Danish University Antidepressant Group. 1990. Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 18:289–299.

Davidson JR, Abraham K, Connor KM, McLeod MN. 2003. Effectiveness of chromium in atypical depression: A placebo-controlled trial. Biol Psychiatry 1;53(3):261–264.

Fieve RR, Platman SR, Plutchik RR. 1968. The use of lithium in affective disorders. I. Acute endogenous depression. Am J Psychiatry 125(4):487–491.

Friedman C, Mowbray MS, Hamilton VJ. 1961. Imipramine (Tofranil) in depressive states: A controlled trial with inpatients. J Ment Sci 107:948–953.

Geddes J, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. 2003. Relapse prevention with antidepressant drug treatment in depressive disorders: A systematic review. Lancet 361:653–661.

Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. 2004. Antidepressants for bipolar depression: A systematic review of randomized, controlled trials. Am J Psychiatry 161(9):1537–1547.

Goodwin FK, Murphy DL, Dunner DL, Bunney WE. 1972. Lithium response in unipolar versus bipolar depression. Am J Psychiatry 129:44–47.

Guelfi JD, Ansseau M, Timmerman L, Korsgaard S. 2001. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 21(4):425–431.

Hellerstein DJ, Yanowitch P, Rosenthal J, Samstag LW, Maurer M, Kasch K, Burrows L, Poster M, Cantillon M, Winston A. 1993. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 150(8):1169–1175.

Jarrett RB, Schaffer M, McIntire D, Witt-Browder A, Kraft D, Risser RC. 1999. Treatment of atypical depression with cognitive therapy or phenelzine: A double-blind, placebo-controlled trial. Arch Gen Psychiatry 56(5):431–437.

Katon W, Russo J, Frank E, Barrett J, Williams JW Jr, Oxman T, Sullivan M, Cornell J. 2002. Predictors of nonresponse to treatment in primary care patients with dysthymia. Gen Hosp Psychiatry 24(1):20.

Keck PE Jr, Wilson DR, Strakowski SM, McElroy SL, Kizer DL, Balistreri TM, Holtman HM, DePriest M. 1995. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. Clin Psychiatry 56(10):466–470.

Kocsis JH, Frances AJ, Voss C, Mann JJ, Mason BJ, Sweeney J. 1988. Imipramine treatment for chronic depression. Arch Gen Psychiatry 45(3):253–257.

Larsen JK, Gjerris A, Holm P, Anderson J, Bille A, Christensen EM, Hoyer E, Jensen H, Mejlhede A, Langagergaard A. 1991. Moclobemide in depression: A randomized, multicentre trial against isocarboxazide and clomipramine emphasizing atypical depression. Acta Psychiatr Scand 84(6):564–570.

Lima MS, Hotopf M. 2003. Benefits and risks of pharmacotherapy for dysthymia: A systematic appraisal of the evidence. Drug Saf 26(1):55–64.

Lonnqvist J, Sihvo S, Syvalahti E, Kiviruusu O. 1994. Moclobemide and fluoxetine in atypical depression: A double-blind trial. J Affect Disord 32(3):169–177.

Markowitz JC. 1994. Psychotherapy of dysthymia. Am J Psychiatry 151(8):1114–1121.

McGrath PJ, Stewart JW, Janal MN, Petkova E, Quitkin FM, Klein DF. 2000. A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. Am J Psychiatry 157(3):344–350.

Miller NL, Kocsis JH, Leon AC, Portera L, Dauber S, Markowitz JC. 2001. Maintenance desipramine for dysthymia: a placebo-controlled study. J Affect Disord 64(2–3):231–237.

Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. 2001. Double-blind, placebo-

controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 158:906–912.

Pande AC, Birkett M, Fechner-Bates S, Haskett RF, Greden JF. 1996. Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 15;40(10):1017–1020.

Parker G, Roy K, Wilhelm K, Mitchell P. 2001. Assessing the comparative effectiveness of antidepressant therapies: A prospective clinical practice study. J Clin Psychiatry 62(2):117–125.

Peet M. 1994. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. Br J Psychiatry 164:549–550.

Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG Jr, Bernstein HJ, Biggs M, Bailine SH, Kellner CH. 2001. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT 17(4):244–253.

Post RM, Altshuler LL, Frye MA, Suppes T, Rush AJ, Keck PE Jr, McElroy SL, Denicoff KD, Leverich GS, Kupka R, Nolen WA. 2001. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. Bipolar Disord 3(5):259–265.

Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein. 1993. Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. Br J Psychiatry Suppl(21):30–34.

Ravindran AV, Anisman H, Merali Z, Charbonneau Y, Telner J, Bialik RJ, Wiens A, Ellis J, Griffiths J. 1999. Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: Clinical symptoms and functional impairments. Am J Psychiatry 156(10):1608–1617.

Ravindran AV, Guelfi JD, Lane RM, Cassano GB. 2000. Treatment of dysthymia with sertraline: A double-blind, placebo-controlled trial in dysthymic patients without major depression. J Clin Psychiatry 61(11):821–827.

Ravizza L. 1999. Amisulpride in medium-term treatment of dysthymia: a six-month, double-blind safety study versus amitriptyline.AMILONG investigators. J Psychopharmacol 13(3):248–254.

Roose SP, Glassman AH, Attia E, Woodring S. 1994. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 151(12):1735–1739.

Rothschild AJ, Bates KS, Boehringer KL, Syed A. 1999. Olanzapine response in psychotic depression. J Clin Psychiatry 60(2):116–118.

Rothschild AJ, Samson JA, Bond TC, Luciana MM, Schildkraut JJ, Schatzberg AF. 1993. Hypothalamic-pituitary-adrenal axis activity and 1-year outcome in depression. Biol Psychiatry 15;34((6)):392–400.

Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Andersen SW, Van Campen LE, Sanger TM, Tollefson G. 2004. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. J Clin Psychopharmacol 24(4):365–373.

Sachs GS, Later B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF. 1994. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 55:391–393.

Schweitzer I, Tiller J, Maguire K, Davies B. 1989. Treatment of atypical depression with moclobemide: A sequential double controlled study. Int J Clin Pharmacol Res 9(2):111–117.

Sogaard J, Lane R, Latimer P, Behnke K, Christiansen PE, Nielsen B, Ravindran AV, Reesal RT, Goodwin DP. 1999. A 12-week study comparing moclobemide and sertraline in the treatment of outpatients with atypical depression. J Psychopharmacol 13(4):406–414.

Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, Perel JM, Rossi AJ, Soloff PH. 1985. The pharmacological treatment of delusional depression. Am J Psychiatry 142(4):430–436.

Stewart JW, Quitkin FM, McGrath PJ, Rabkin JG, Markowitz JS, Tricamo E, Klein DF. 1988. Social functioning in chronic depression: effect of 6 weeks of antidepressant treatment. Psychiatry Res 25(2):213–222.

Thase ME, Entsuah AR, Rudolph RL. 2001. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 178:234–241.

Thase ME, Friedman ES. 1999. Is psychotherapy an effective treatment for melancholia and other severe depressive states? J Affect Disord 54(1–2):1–19.

Tignol J, Stoker MJ, Dunbar GC. 1992. Paroxetine in the treatment of melancholia and severe depression. Int Clin Psychopharmacol 7(2):91–94.

Tiller J, Schweitzer I, Maguire K, Davies B. 1989. A sequential double-blind controlled study of moclobemide and diazepam in patients with atypical depression. J Affect Disord 16(2–3):181–187.

Tzanakaki M, Guazzelli M, Nimatoudis I, Zissis NP, Smeraldi E, Rizzo F. 2000. Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. Int Clin Psychopharmacol 15:29–34.

Vanelle JM, Attar-Levy D, Poirier MF, Bouhassira M, Blin P, Olie JP. 1997. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry 170:345–350.

Versiani M, Amrein R, Stabl M. 1997. Moclobemide and imipramine in chronic depression (dysthymia): An international double-blind, placebo-controlled trial. Int Clin Psychopharmacol 12(4):183–193.

Versiani M. 1996. Pharmacotherapy of dysthymia: A controlled study with imipramine, moclobemide or placebo. Neuropsychopharmacology 10:298.

Vieta E, Martinez-Aran A, Goikolea JM, Torrent C, Colom F, Benabarre A, Reinares M. 2002. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 63:508–512.

Von Frenckell R, Ansseau M, Serre C, Sutet P. 1990. Pooling two ontrolled comparisons of milnacipran (F2207) and amitriptyline in ndogenous inpatients. A new approach in dose ranging studies. Int Clin Psychopharmacol 5:49–56.

Woelk H. 2000. Comparison of St John's wort and imipramine for treating depression: Randomised controlled trial. Br Med J 2;321(7260):536–539.

Wolfersdorf M, Barg T, Konig F, Leibfarth M, Grunewald I. 1995. Paroxetine as antidepressant in combined antidepressant-neuroleptic therapy in delusional depression: observation of clinical use. Pharmacopsychiatry 28(2):56–60.

Zarate CA Jr, Rothschild A, Fletcher KE, Madrid A, Zapatel J. 2000. Clinical predictors of acute response with quetiapine in psychotic mood disorders. J Clin Psychiatry 61(3):185–189.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 38–43

LECTURE

Is the practice of ECT ethical?

MAX FINK

Department of Psychiatry, School of Medicine, Stony Brook University, Long Island, New York, NY, USA

Abstract
The ethical principles of medical care are beneficence (doing good), non-maleficence (not doing harm), autonomy (right to refuse or accept treatment), and justice (equality of opportunity). The present practice of ECT meets standards for beneficence, non-maleficence, and autonomy. In many nations, however, the principle of justice is not respected, leading to unavailability of ECT, increased suffering and prolonged illness. The signs of improvement are slowly surfacing in the greater recognition of the efficacy of ECT, greater tolerance to its use, and in establishing treatment standards.

Key words: *Beneficence, non-maleficence, autonomy, justice, electroconvulsive therapy*

Introduction

Although ECT is almost universally regarded as an effective treatment for patients with the most severe psychiatric illnesses, it is also the most stigmatized treatment in medicine. As a consequence, it is hardly available for patients in the most need. The education of medical students and psychiatric residents is so restricted that medical practitioners cannot advise their patients effectively. Technical training is haphazard, making it difficult to find trained therapists. The public sees ECT as controversial, painful, and frightening, leading legislatures to limit its use (Ottosson and Fink 2004).

The negative attitudes to ECT have roots in misperceptions about the treatment and about psychiatric illness. ECT is a complex procedure that is considered old-fashioned and socially incorrect. Some believe that it is still forced on the patient, used by the state to subjugate its unruly citizens, and that memory disturbances are so severe and so persistent that no rational human being would undergo this procedure, no matter how well intended.

The central skill in psychiatric practice is talking, augmented by prescriptions for medications. ECT, by contrast, requires the laying on of the hands in a complex procedure that calls on the skills of a medical team. It is an old treatment with a persisting image of its earliest days, before the introduction of anaesthesia, oxygenation, and consent in its practice. In the first years, the experience was frightening and the risk of bone fracture real. Since sedation and muscle paralysis became standard aspects of ECT in Western societies, these risks are no longer present (Fink 1999; Ottosson and Fink 2004). The technique of stimulation has been refined, and superficial anaesthesia with muscular relaxation and oxygenation are in wide use (Abrams 2002). Treatments are much more lenient than pictured by the public and presented by film and television.

Many believe that ECT is forced upon an unwilling patient, as pictured in the film *One Flew Over the Cuckoo's Nest.* But such is not acceptable practice as individual consent is required for treatments. Only when patients are considered incompetent by reason of a severe psychiatric disturbance is ECT proposed without individual consent. At such times, the laws of the state for the application of life-saving procedures may be invoked and the patient treated.

Patients awaken confused with each treatment. Like the bleeding of surgery, the immediate and transient confusion and memory loss for the events surrounding the treatments is an essential feature of ECT. In the weeks of recovery, however, memory returns and patients are able to recall their history and undertake new learning as well as they did before. In the overall picture of the thousands of patients treated with ECT each year, the memory effects are a nuisance rather than an unassailable obstacle to its use.

Correspondence: Max Fink, P.O. Box 457, St James, NY 11780, USA. Tel: +1 631 862 6651; E-mail: mfink@sunysb.edu

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030054

After the Second World War, as Western society faced the horrors of the experimentation of Nazi doctors, codes of ethical conduct were developed. The Nuremberg Code of 1947 established guidelines for proper treatment and ethical experimentation in humans. The code was modified in many ways, the most recent being the revision by the World Medical Association in 2002. For psychiatric patients, the 1977 Declaration of Hawaii of the World Psychiatric Association and the amendments in the Declaration of Madrid of 1996 are the most relevant. Each guide calls on the medical community to fulfil the precepts of ethical codes that go back to the oath of Hippocrates (Ottosson and Fink 2004).

Principles of medical ethics

The four principles of beneficence, nonmaleficence, autonomy, and justice are central to ethical conduct (Beauchamp and Childress 2002). Beneficence is the principle that 'doing good' is essential to medical care. Not doing harm is the rule of nonmaleficence. Autonomy respects the right of each person to decide whether to accept or reject treatment; it requires respect for each person as a unique human being with responsibility for his own body. Justice asks that all human beings be treated equally, without regard to social or financial factors, and that the most effective treatments be offered to all.

Does the practice of electroconvulsive therapy meet the standards of medical ethics?

Beneficence. A treatment that offers effective benefits at minimal risk is considered beneficent. ECT is widely recognized as an effective treatment for a lengthy list of conditions. It is often reserved for use when all other treatments have failed, and is still effective even under this compelling hurdle. The effective indications are major depression, especially its psychotic form (Petrides et al. 2001; UK ECT Review Group 2003) and catatonia, especially its malignant form (Fink and Taylor 2003). ECT relieves mania (Mukherjee et al. 1994) and some forms of schizophrenia (Fink and Sackeim 1996). The risk of suicide decreases after ECT (Prudic and Sackeim 1999; Kellner et al. 2005).

The merits of these uses are well documented. A meta-analysis of 18 random-controlled trials (1144 participants) of various forms of ECT and medications over five decades found ECT more effective than pharmacotherapy (UK ECT Review Group 2003).

ECT is particularly effective for patients with psychotic depression. In a study of 253 patients with major depression treated with bilateral ECT, 77 were psychotic and 176 non-psychotic. The remission rate was 87% for the study completers, 96% for the psychotic depressed, and 83% for the non-psychotic depressed (Petrides et al. 2001). Similar findings are reported by Birkenhäger et al. (2003) and Kho et al. (2003). These findings confirm the early reports that remission in psychotic depression is achieved in 34% of patients treated with TCAs alone, 51% with antipsychotic agents alone, 77% with the combined use of these drugs, and 82% with ECT alone (Kroessler 1985).

ECT achieves remission rapidly and sharply reduces the duration of illness. In the collaborative four-hospital ECT study, known as the CORE trial, remission of severe depression was achieved in 5% in 1 week (three ECT), 45% in 2 weeks, and 81% in 3 weeks (Figure 1).

The impact on suicidal risk is even more compelling. In the CORE trial, the suicide risk was assessed by item 3 in the 24-item Hamilton Depression Rating Scale. The suicide risk of patients rated as high-risk was rapidly relieved to no risk in 38% in 1 week, 61% in 2 weeks, and 81% in 4 weeks of treatment (Figure 2).

These data are supported by similar findings in the treatment of mania, malignant catatonia, neuroleptic malignant syndrome, and schizophrenia (Abrams 2002; Fink and Taylor 2003; Ottosson and Fink 2004).

The practice of ECT complies with the principle of beneficence.

Non-Maleficence. When ECT was first introduced, the risks of death, fractures, and tardive seizures were commonplace, but these are now alleviated. Fear of treatments and fracture has been relieved by anaesthesia and muscle relaxants (Abrams 2002). The death rate in ECT is negligible, being less than that of normal pregnancy (Nuttall et al. 2004).

The most discussed risk of ECT is the development of persistent memory loss. When ECT was introduced, confusion and complaints of memory loss were common; indeed, the losses were first considered an explanation of the mechanism of the treatment (Fink 1999). But, in time, the currents, dosing, and electrode placement were optimized; active ventilation with oxygen was established as routine; and the frequency and numbers of treatments balanced to achieve greatest benefit at least risk (Abrams 2002; Ottosson and Fink 2004).

Gaps in memory for the times of treatment, especially impaired recollection of personal and public events, are frequent. These gaps, however, disappear within a few weeks after the completion of the treatment. Many patients even experience their memory as improved compared to the difficulties

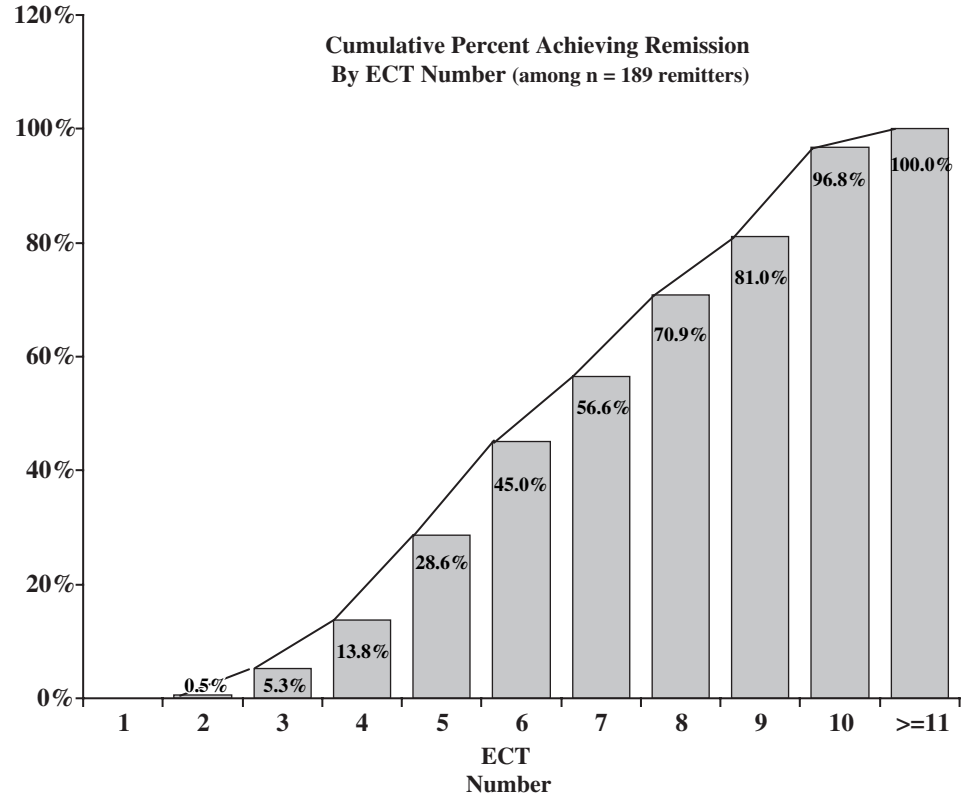


Figure 1. Cumulative percentage of unipolar depressed patients achieving remission with ECT. From the Core study (Husain et al. 2001).

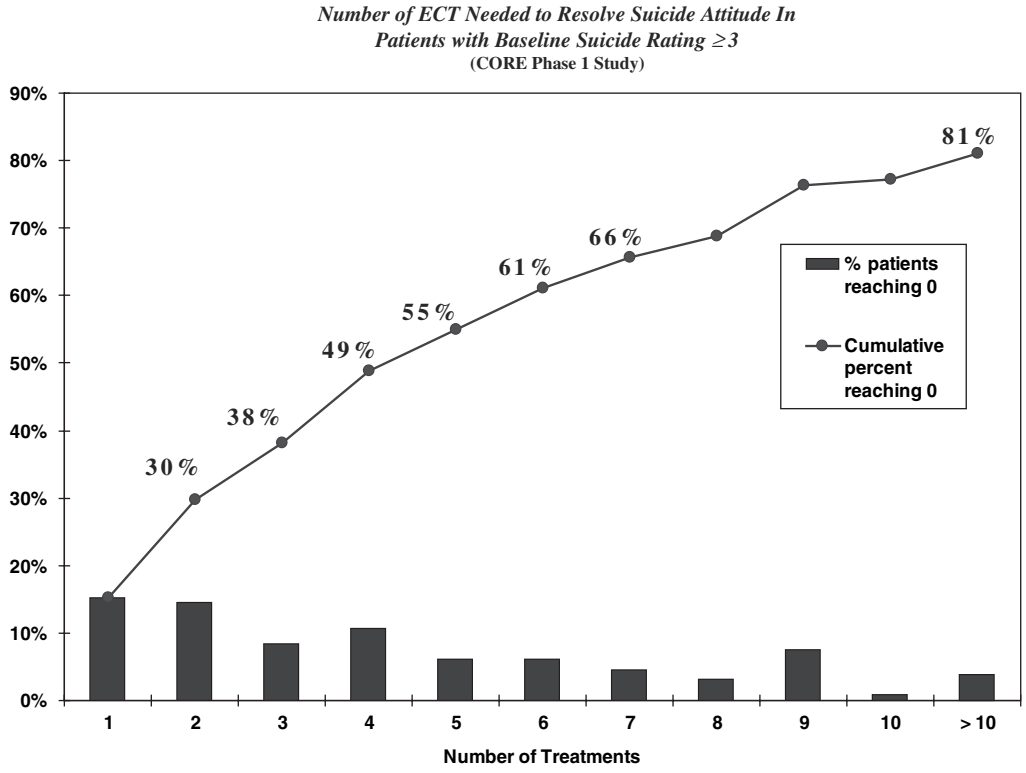


Figure 2. Conversion of high risk suicide item in the Hamilton Depression Scale to zero. From a CORE study (Kellner et al. 2005).

associated with the illness. Prolonged disturbance is rare, and should it occur, the role of ECT is uncertain (APA 1990; Abrams 2002; Ottosson and Fink 2004). Most patients experience their memory impairment as a small nuisance in comparison with the relief of their psychiatric disability.
ECT is consistent with the ethical principle of non-maleficence, offering minimal risk in the face of extraordinary relief of illness.

Respect for autonomy. The practice of ECT is burdened by worldwide stigmatization. Film, television, and attacks from anti-psychiatry lay groups such as the Church of Scientology have poisoned the well of public opinion. Many see the treatment as forced on patients, against their will, as pictured in *One Flew Over the Cuckoo's Nest* and in *The Snakepit*. As informed consent is a requirement for all health care, it applies to psychiatry, and is particularly pertinent to ECT. Before beginning a course of ECT, almost all patients have failed multiple trials of other treatments. They are well acquainted with consent procedures. For ECT, however, voluntary consent is essential. Patients are told the reasons why the treatment is recommended, the benefits and risks that are anticipated, and the efficacy and safety of ECT compared to alternative treatments. A written consent describes the procedure and the reasons why the treatment is offered, as well as who is responsible for the procedure. The consent is signed by the patient in the presence of a witness, usually a family member, and becomes an essential part of the patient's record (APA 1978, 1991; Abrams 2002).

When patients are considered incapable of giving an informed voluntary consent by reason of their mental illness, they may be treated after judicial authorization, following the laws of the community in which the patient resides. Nowadays, nearly all patients give voluntary consent for ECT. In two states of the United States, all courses of ECT are required to be registered with the state and it is possible to determine how many patients are voluntarily treated and how many under court mandate. From 1 to 2% of ECT-treated patients are treated with judicial consent (Reid et al. 1998; Kramer 1999).
Modern ECT practice complies with the principle of respect for autonomy.

Principle of justice. The principle of justice calls for ECT to be available to all the ill that need it, regardless of age, gender, social and financial status, or nation, hospital, or catchment area. The decisive factor is the need for the treatment. World-wide, the adherence to this principle is spotty, and even within a nation the availability is uneven. In the United States, ECT is available at academic hospitals, but is hardly available at state, municipal, or Veterans Administration hospitals (Hermann et al. 1995). Training in practice is limited, so that only 8% of the members of the American Psychiatric Association used or were confident in administering ECT (Hermann et al. 1998). Laws in some states in the US so restrict the use of ECT that psychiatrists cannot give appropriate care (Ottosson and Fink 2004). Treatment algorithms offered by expert committees recommend trial after trial of medication before ECT, which is considered the last resort, disadvantaging and encouraging prolonged suffering in depressed patients (Crismon et al. 1999). Similar unjustice is reported from European countries (Koukopoulos, 1993; Benadhira and Teles 2001; Philpot et al. 2002).

Modern psychiatric care is increasingly focused on the prescription of medications. The dependence on medication so dominates clinical practice that even when ECT is the compelling primary treatment for the condition, the patients are offered medication trials, often one failed trial after another to the patient's detriment. ECT is more effective than medication in psychotic depression, malignant catatonia and neuroleptic malignant syndrome, catatonic schizophrenia, manic delirium and rapid cycling mania. The failure to offer ECT as a primary treatment in patients with these illnesses is unjust.
Regretfully, it must be concluded that the practice of ECT in many countries does not comply with the principle of justice.

Discussion

The modern practice of ECT is based on confident patient–psychiatrist relationships. For many patients, their own experience with ECT, or their witnessing the benefits in other patients, or their faith in their physician suffices to encourage its use and their voluntary consent. By personal experience, they are unhappy with the limited benefits of medications and psychotherapy. After previous ECT, they experienced only transient problems with their memory. Patients consent to treatment and patients at the same department are treated equally.

Many efforts are being made to find a more elegant and less distressing treatment, and it may not be long before ECT is replaced by an equally effective and less controversial treatment. As long as ECT has an evidence-based superiority over other treatments, however, it must be utilized for the benefit of patients. Proper use not only assures patients of an effective treatment but is considerate of health care costs. The widespread non-compliance with the principle of justice in the practice of

ECT violates medical ethical principles and the UN Declaration of Human Rights that human beings are equal in dignity and in rights.

What is to be done to rectify the injustice of present views of ECT is unclear. The national surveys that show distorted availability encouraged greater interest, reflected by greater usage in German speaking parts of Europe and the publication of a new German textbook (Baghai et al. 2004). Comparisons of ECT and medications increasingly recognize the proper role of ECT and greater interest is shown in optimizing treatment after ECT, including continuation ECT. While training is still on an *ad hoc* basis, the UK Royal College of Psychiatrists has established training programs and a voluntary certification of those treatment sites that meet national standards (Caird et al. 2004). The promoters of new devices to replace ECT by magnetic stimulation, vagus nerve stimulation, and deep brain stimulation, who loudly trumpet the memory effects of ECT as a principal justification for their efforts, have been unable to establish an efficacy for their devices to match that of ECT. Attention is slowly returning to ECT. The President of the WFSBP, Dr Carlos Hojaij, established a Task Force on ECT and invited teaching sessions at the 2004 Sydney and Athens meetings. On the other hand, treatment algorithms in the WFSBP treatment guidelines inappropriately relegate ECT to a 'last resort' position, following the capricious guidelines of US, UK and Canadian authors. One can be more optimistic that as the interest in evidence-based medicine increases, the proper role of ECT will be recognized, and the present injustices in usage and distribution of facilities will improve.

Acknowledgement

I am indebted to Prof. Jan-Otto Ottosson of Götsborg, Sweden for defining the ethical issues discussed here.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Abrams R. 2002. Electroconvulsive therapy. 4th ed. New York: Oxford University Press.

American Psychiatric Association. 1978. Electroconvulsive therapy. Task Force Report #14. Washington, DC: American Psychiatric Association.

American Psychiatric Association. 1990. The practice of electroconvulsive therapy: Recommendations for treatment, training and privileging. Washington, DC: APA Press.

Baghai TC, Frey R, Kasper S, Möller H-J. 2004. Elektrokonvulsionstherapie. Vienna: Springer.

Beauchamp TL, Childress JF. 2001. Principles of biomedical ethics. 5th ed. New York: Oxford University Press.

Benadhira R, Teles A. 2001. Current status of electroconvulsive therapy in adult psychiatric care in France (in French). Encephale 27:129–136.

Birkenhäger TK, Pluijms EM, Lucius SAP. 2003. ECT response in delusional versus non-delusional depressed inpatients. J Affect Disord 74:191–195.

Caird H, Worrall A, Lelliott P. 2004. The electroconvulsive therapy accreditation service. Psychiatr Bull 28:257–259.

Crismon ML, Trivedi M, Pigott T, Rush AJ, Hirschfeld RM, Kahn DA, DeBattista C, Nelson JC, Nierenberg AA, Sackeim HA, Thase ME. 1999. The Texas Medication algorithm project: Report of the Texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry 60:142–156.

Fink M. 1999. Electroshock: Restoring the mind. New York: Oxford University Press.

Fink M, Sackeim HA. 1996. Convulsive therapy in schizophrenia. Schizophrenia Bull 22:27–39.

Fink M, Taylor MA. 2003. Catatonia. A clinician's guide to diagnosis and treatment. Cambridge UK: Cambridge University Press.

Hermann RC, Dorwart RA, Hoover CW, Brody J. 1995. Variation in ECT use in the United States. Am J Psychiatry 152:869–875.

Hermann RC, Ettner SL, Dorwart RA, Hoover CW, Yeung E. 1998. Characteristics of psychiatrists who perform ECT. Am J Psychiatry 155:889–894.

Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, Biggs MM, O'Connor K, Rasmussen K, Litle M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, Kellner CH. 2004. Speed of response and remission in major depressive disorder with acute ECT: A Consortium for Research in ECT (CORE) Report. J Clin Psychiatry 65:485–481.

Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, Mueller M, Bernstein H, Rasmussen K, O'connor K, Smith G, Rush AJ, Biggs M, McClintock S, Bailine S, Malur C. 2005. Relief of expressed suicidal intent by ECT: A Consortium for Research in ECT Study. Am J Psychiatry 162:977–982.

Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. 2003. A meta-analysis of electroconvulsive therapy efficacy in depression. J ECT 19:139–147.

Koukopoulos A. 1993. ECT: Why so little in Italy? Int J Psychiatr Behav Sci 3:79–81.

Kramer BA. 1999. Use of ECT in California, revisited: 1984–1994. J ECT 15:245–251.

Kroessler D. 1985. Relative efficacy rates for therapies of delusional depression. Convulsive Ther 1:173–182.

Lisanby SH, editor. 2004. Brain stimulation in psychiatric treatment. Washington DC: American Psychiatric Publishing Co.

Mukherjee S, Sackeim HA, Schnur DB. 1994. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry 151:169–176.

Nuttall GA, Bowersox MR, Douglass SB, McDonald J, Rasmussen LJ, Decker PA, Oliver WC Jr, Rasmussen KG. 2004. Morbidity and mortality in the use of electroconvulsive therapy. J ECT 20:237–241.

Ottosson J-O, Fink M. 2004. The ethical dilemma of ECT. New York: Brunner-Routledge.

Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG Jr, Bernstein HJ, Biggs M, Bailine SH, Kellner CH. 2001. ECT

remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT 17:244–253.

Prudic J, Sackeim HA. 1999. Electroconvulsive therapy and suicide risk. J Clin Psychiatry 60(Suppl 2):104–110.

Philpot M, Treloar A, Gormley N, Gustafson L. 2002. Barriers to the use of electroconvulsive therapy in the elderly: a European survey. Eur Psychiatry 17:41–45.

Reid WH, Keller S, Leatherman M, Mason M. 1998. ECT in Texas: 19 months of mandatory reporting. J Clin Psychiatry 59:8–13.

UK ECT Review Group. 2003. Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. Lancet 361:799–808.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 44–48

LECTURE

Childhood meningitis increases the risk for adult schizophrenia*

ANDRÉ L. ABRAHAO[1], ROBERTO FOCACCIA[2] & WAGNER F. GATTAZ[1]

[1]*Departament of Psychiatry, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil, and* [2]*Instituto de Infectologia Emílio Ribas, Sao Paulo, Brazil*

Abstract

Objective: We investigated the hypothesis that a meningitic infection in childhood may increase the risk of a psychiatric disorder in adulthood. *Method:* We conducted a follow-up study of 190 individuals affected by a meningitis infection the first 4 years of life, during an epidemic in São Paulo, Brazil, between 1971 and 1974. As a control group, we investigated 156 siblings of the meningitis patients who were not affected by meningitis at childhood. *Results:* In the 190 cases of meningitis, we found eight (4.2%) cases of schizophrenia against none in the controls, and 40 (21.0%) cases of life occurrence of psychotic symptoms compared to 12 (7.6%) cases in the control group ($P < 0.001$). We found no differences between the two groups regarding the occurrence of other psychiatric disorders and of neurological soft signs. *Conclusion:* Meningitis during childhood significantly increased the risk of schizophrenia in particular in adulthood, and of psychosis in general.

Key words: *Meningitis, childhood infection, schizophrenia, risk factor*

Introduction

In the last century, several authors discussed the participation of infectious diseases in the risk for schizophrenia. Kraepelin considered that 'infections in the years of development might have a causal importance' for schizophrenia (Wright et al. 1999). Menninger, in 1928, in a review of the studies of his time about infectious diseases and psychiatric illness, related that cases of acute meningitis, encephalitis, typhoid fever, recurrent fever, typhus, influenza, malaria, tuberculoses, gastrointestinal infections and septicemia were frequently followed by an acute and transitory episode of a schizophreniform syndrome or a schizophrenic disease in its more specific sense. Rantakallio et al. (1997), in a study comparing individuals with a central nervous system infection during childhood with a control group followed-up until age 27 years, found an increase of schizophrenia in the infection group (O.R. = 4.2). Leask et al. (2002), in an investigation of data from medical school examinations, reported that childhood meningitis increased the risk of schizophrenia (O.R. = 7.8) and mood disorders with psychotic symptoms (O.R. = 7.7) in adulthood.

There is number of studies also showing the influence of pre-natal infections increasing the risk for psychiatric illnesses. Influenza, rubella, herpes virus and cytomegalovirus have been studied and positive findings have been shown (Brown and Susser 1999). Influenza, the most studied prenatal infection, shows some contradictory findings (reviewed by Wright et al. 1999). Brown et al. (2001) found that about 21% of patients who had presented clinical manifestations of congenital rubella have developed a schizophrenic spectrum disorder in adulthood.

In the city of São Paulo, Brazil, there was an meningococcal meningitis epidemic from 1971 to 1974 (Iversson 1976). Most of the cases (90%) were admitted to the Emilio Ribas Hospital, a public and university hospital, specialized in infectious diseases. In the present study, we investigated the prevalence of psychiatric diagnoses in general in a sample of adults who, during the epidemic period, were admitted up to the age of 4 years to this hospital with the diagnosis of meningitis.

Correspondence: Wagner F. Gattaz, M.D., Full Professor of Psychiatry & Director of the Laboratory of Neuroscience, Department of Psychiatry, Faculty of Medicine, University of Sao Paulo, Rua Dr. Ovidio Pires de Campos 785, 05403-010 Sao Paulo, SP, Brazil. Tel: +5511 3069 8010. E-mail gattaz@usp.br

*Part of these results has already been published in the *Eur Arch Psychiatry Clin Neurosci* 254:23–6, 2004.

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030063

Material and methods

Finding the subjects

The database used was the file of microfilmed medical registers from Emílio Ribas Hospital. From these registers, we obtained the names of the patients, of their parents and the patients' age when admitted. Then a search was done in the database of the telephone company, on the web site (www.telefonica.net.br), for the name of the patient and of his parents. When a subject was found, he was informed about our study and invited to an interview at the Institute of Psychiatry of the University of Sao Paulo Medical School. We also asked to the interview one sibling of the patient, preferably older, but aged as close as possible to the patient, and who had not been affected by meningitis in childhood. The siblings composed the control group. The cases (meningitis) and the controls (siblings) received R$50 ($\pm$U$20) each, as a compensation for coming to the interview.

Interviews

A standard psychiatric diagnostic interview was undertaken based on the ICD-10 Checklist (Janca and Hiller 1996), and the presence of neurological soft signs was tested with the neurological evaluation scale from Buchanan and Heinrichs (1989).

Reliability of the diagnoses

Since only one psychiatrist has interviewed all patients, and he was aware whether they were cases or siblings, we tested the reliability of the diagnoses. Four psychiatrists received a written resume of the clinical histories of all individuals. The resumes were codified, not identifying who was case or sibling. All four doctors showed an agreement in their diagnoses, with the main researcher higher than 80% in the Kappa test.

Sample description

When the microfilmed files were analysed, 4951 registers were found from patients admitted with meningitis, aged 4 or less, from January 1970 to December 1975. Up to now, 1,890 files had telephone searches, and 361 (18.1%) individuals were localized. Of these, 190 (52.6%) cases and 156 (82.1%) controls agreed and came to the interview.

Table I presents the demographic and social economical data of cases and controls. No remarkable difference was found, except that (interestingly) in the cases income was significantly higher than in their siblings.

Statistics

For data analysis, the following statistics were used, as needed: Kolmogorov–Smirnov test, Breslow–Day Test,Mann–Whitney test, Chi-square, *t*-test, Kappa test, test for the difference of signs and stratified analysis. The data are presented as average $\pm$ standard deviation.

Results

Individuals with meningitis in childhood had a higher prevalence of schizophrenia and of psychoses in general, as well as more neurological disorders and higher comorbidity rates, compared to their siblings without childhood meningitis (Tables II, III and IV).

Since deafness may increase the risk for psychoses (Altshuler and Sarlin 1969), we compared the diagnoses between three groups: controls, cases with any hearing deficit and cases without hearing deficit. Basically, all the differences shown before are maintained here, with a predominance of psychoses in general in the meningitis cases (Table V).

There was no association between neurological diagnoses and psychosis. If we exclude from the analyses cases and controls with neurological diagnoses, the difference remains as before, with more psychosis and more schizophrenia in the meningitis group (Table VI).

Soft signs

There were no differences in the neurological soft signs between cases (7.4 ± 4.1) and controls (7.8 ± 4.2). However, soft signs ratings were higher in individuals with psychoses (8.9 ± 3.8) than in individuals without psychoses (7.3 ± 4.2, $P < 0.01$).

Age of meningitis

The age at the time of meningitis infection was lower in cases with psychotic symptoms (21.9 ± 13.2 months) than in cases without psychotic symptoms (27.4 ± 15.3 months, $P < 0.05$).

Table I. Socio-demographic characteristics of cases and controls.

	Cases ($n = 190$)	Siblings ($n = 156$)
Men	88 (46.3%)	56 (35.9%)
Women	102 (53.7%)	100 (64.1%)+
Age (years)	29.2 ± 1.6	30.0 ± 5.9
Income (in Reais)	R$ 948.00 ± 943.00*	R$ 739.00 ± 828.00
Years at school	11.5 ± 3.7	11.3 ± 4.0

*$P < 0.05$, +$P < 0.10$.

Table II. General prevalence of neurological and psychiatric disorders.

	Cases ($n=190$)	Siblings ($n=156$)
All psychiatric disorders	117 (61.5%)	93 (59.6%)
All neurological disorders	47 (24.7%)***	9 (5.7%)

***$P<0.001$.

Discussion

Our main finding was that meningitis in childhood increased the risk for psychosis in adulthood by 4.6 times, and for schizophrenia in particular by 4.4 times, whereas no changes were found in the risk for other psychiatric disorders.

An interesting aspect of our study is that the control group was formed by siblings of the patients, who did not have had meningitis in early childhood. So, to a considerable extent, both groups were very well matched regarding aspects such as genetic, socio-cultural, economical and nutritional backgrounds. Thus, the difference between our groups of cases and controls was, basically, the presence or absence of meningitis in the first four years of life.

Our findings are similar to the studies of postnatal infections increasing the risk for psychosis (Rantakallio et al. 1997; Leask et al. 2002). Our cases with psychotic symptoms showed more neurological soft signs as compared to the siblings group, and this also agrees with the literature (Brown et al. 2001; Leask et al. 2002).

The mean age of meningitis was lower in the cases that presented psychotic symptoms than in cases without psychotic symptoms, suggesting that vulnerability to psychosis may be increased by earlier insults during the maturation of the brain. However, the mechanisms by which it happens are not yet clarified. In animal experiments, Borrell et al. (2002) found that the injection of a bacterial endotoxin (lipopolysacccharide, LPS) to pregnant female rats disrupts the prepulse inhibiton (PPI) of the acoustic startle reflex in the offspring, and this effect could be reversed by antipsychotic drugs. This finding is of interest because PPI is an accepted animal model for schizophrenia.

Table IV. Neurological disorders.

	Case ($n=190$)	Siblings ($n=156$)
No neurological diagnosis	143 (75.2%)***	147 (94.2%)
Deafness (partial and total)	18 (9.4%)***	1 (0.6%)
Motor deficit	9 (4.7%)**	0 (0%)
Headache NOS	12 (6.3%)	7 (4.5%)
Epilepsy	6 (3.1%)	1 (0.6%)
Visual deficit	1 (0.5%)	2 (1.2%)
Other neurological disorders (visual deficit related to meningitis, anosmia, nystagmus cross-eye and tremors)	2 (1.0%)	0 (0%)

**$P<0.01$; ***$P<0.001$.

The prevalence of psychiatric disorders in our study, 60.3% in siblings and 62.4 in controls, is above what is found in epidemiological studies done in representative samples of the population in Brazil (Andrade et al. 1999 reported 45.6%) and in the USA, where Robins and Regier (1990), in the Epidemiological Catchment Area Study (ECA), report 32% of total psychiatric morbidity. In our study, it is likely that the call to a medical interview in the University Hospital may have selected a sample in higher need of medical-psychiatric care, therefore with a higher morbidity, among those who answered the call. Nevertheless, our figures are similar to those reported by Brown et al. (2001), who found 58.5% overall psychiatric morbidity in the rubella study.

Some studies pointed to an association between deafness and increased risk for psychosis (Altshuler

Table III. Psychiatric diagnosis grouped.

	Cases ($n=190$)	Siblings ($n=156$)
Without any diagnoses	73 (38.5%)	63 (40.4%)
Anxiety disorders (*F* 40.1, *F* 40.2, *F* 41.0, *F* 41.1, *F* 41.2, *F* 42.9)	71 (37.3%)	55 (35.2%)
Personality disorders (*F* 60.3, *F* 60.5)	8 (4.2%)	3 (1.9%)
Alcohol and drugs abuse (*F* 10.1, *F* 10.2, *F* 12.1, *F* 14.2)	14 (7.3%)	12 (7.6%)
Mood disorder without psychotic symptoms (*F* 32.0, *F* 32.1, *F* 32.2, *F* 33.0, *F* 33.1, *F* 33.2, *F* 34.0 *F* 34.1 e *F* 31.0)	51 (26.8%)	38 (24.3%)
Mood disorder with psychotic symptoms (*F* 32.3, *F* 33.3)(2)	13 (6.8%)	6 (3.8%)
Schizophrenia (1) (*F* 20.0, *F* 20.5, *F* 20.6)	8 (4.2%)***	0 (0%)
Other psychosis (3) (*F* 29, *F* 10.5, *F* 22.0)	21 (12.1%)**	4 (2.8%)
All psychoses	40 (21.0%)***	12 (7.6%)
Comorbidity	52 (30.0%)**	20 (14.2%)

**$P<0.01$; ***$P<0.001$.

Table V. Psychiatric diagnosis in cases with and without hearing deficit.

	Controls ($n=141$)	Cases with hearing deficit ($n=18$)	Cases without hearing deficit ($n=155$)
Without psychiatric diagnostic	54 (38.3%)	9 (50.0%)	56 (36.1%)
Anxiety disorder	51 (36.1%)	+2 (11.1%)*	60 (38.7%)
Personality disorders	3 (2.1%)	0	5 (3.2%)
Alcohol and drugs	12 (8.3%)	1 (5.6%)	13 (8.4%)
Mood without psychotic symptoms	34 (24.1%)	5 (27.8%)	44 (28.4%)
Mood with psychotic symptoms	4 (2.8%)	1 (5.6%)	12 (7.7%)
Schizophrenia	0	1 (5.6%)	7 (4.5%)*
Other psychosis	4 (2.8%)	1 (5.6%)	20 (12.9%)**
All psychoses	7 (5.0%)	+3 (16.7%)	35 (22.6%)***
Co morbidity	20 (14.2%)	2 (11.1%)	50 (32.3%)***

$+P<0.1$; $*P<0.05$; $**P<0.01$; $***P<0.001$.

and Sarlin 1969). However, in our study the excess of psychosis in the meningitis group is maintained if we left off the cases with partial or full deafness from the analyses (Table V). The differences are also maintained after the exclusion from the analysis of the cases with a neurological diagnosis (Table VI).

In the control group there was a non-significant dominance of women, compared to the group of cases. The onset of schizophrenia in women is about 3 years later then men. In a representative sample, Häfner et al. (1999) report that the average age of appearance of the first negative symptoms of the disease was about 22 years in men and 25 in women, and the age at the first psychotic symptoms was 26.7 and 30.9 years, respectively. However, our sample has an average age of 30.0 ± 5.9 years old, indicating that most of the controls had already passed the risk age for disease onset. Therefore, the excess of women in controls does not contribute to the lower prevalence of psychosis in this group. Besides, the stratified analysis showed that the variation of sex does not contribute to the differences in the occurrence of psychotic diseases in cases and controls. And, finally, comparing only the female individuals we also found more psychoses in women with meningitis than in women without meningitis during childhood (Table VII).

Taken together, our findings add to the body of literature showing that infectious diseases that may affect the brain in childhood do increase the risk for psychosis in adults. The clarification of the mechanisms by which this occurs could shed more light in the understanding of environmental influences in the risk for psychosis.

Table VI. Psychiatric diagnosis in cases and controls without neurological disorders.

	Controls ($n=147$)	Cases without neurological disorders ($n=143$)
Without psychiatric diagnostic	58 (39.4%)	54 (37.7%)
Anxiety disorder	50 (34.0%)	52 (36.3%)
Personality disorders	0	5 (3.5%)*
Alcohol and drugs	10 (6.8%)	9 (6.3%)
Mood without psychotic symptoms	28 (19.0%)	25 (17.5%)
Mood with psychotic symptoms	6 (4.1%)	9 (6.3%)
Schizophrenia	0	7 (4.9%)**
Other psychosis	6 (4.0%)	16 (11.2%)*
All psychoses	12 (8.1%)	29 (20.3%)**
Co morbidity	23 (15.6%)	44 (30.7%)**

$*P<0.05$; $**P<0.01$.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

Table VII. Psychiatric diagnosis in women.

	Siblings ($n=100$ women)	Cases ($n=102$ women)
Without psychiatric diagnostic	30 (30.0%)	26 (25.5%)
Anxiety	40 (40.0%)	53 (51.9%)
Personality disorders	3 (3.0%)	3 (2.9%)
Alcohol and drugs	4 (4.0%)	6 (5.9%)
Mood without psychotic symptoms	35 (35.0%)	39 (38.2%)
Mood with psychotic symptoms	5 (5.0%)	11 (10.8%)
Schizophrenia	0	3 (2.9%)
Other psychosis	4 (4.0%)	15 (14.7%)*
All psychosis	9 (9.0%)	27 (26.4%)**
Co morbidity	16 (16.0%)	38 (37.2%)**

$*P<0.05$; $**P<0.01$; $***P<0.001$; $+P<0.1$.

References

Altshuler K, Sarlin M. 1969. Deafness and schizophrenia: A family study. In: Rainer J, Altshuler K, Kallman F, editors. Family and mental health problems in a deaf population. Springfield, IL: Charles C. Thomas. pp 204–213.

Andrade LH, Lólio CA, Gentil V, Laurenti R. 1999. Epidemiologia dos transtornos mentais em uma área definida de captação da cidade de São Paulo, Brasil. Rev Psiq Clín 26(5, Edição Especial):257–261.

Borrell J, Vela JM, Arevalo-Martin A, Molina-Holgado E, Guaza C. 2002. Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia. Neuropsychofarmacology 26(2):204–215.

Brown AS, Susser ES. 1999. Plausibility of prenatal rubella, influenza, and other viral infections as risk factors for schizophrenia. In: Susser ES, Brown AS, Gorman JM, editors. Prenatal exposures in schizophrenia. Progress in psychiatry series, no. 56. Washington and London: American Psychiatric Press. pp 113–133.

Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM. Prenatal rubella, premorbid abnormalities and adult schizophrenia. Biol. Psychiatry 49:473–486.

Buchanan RW, Heinrichs DW. 1989. The Neurological Evaluation Scale (NES): a structural instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 27(3):335–350.

Häfner H, Maurer K, Löffler W, Heiden W, Stein A, Könnecke R, Hambrecht M. 1999. Onset and prodromal phase as determinants of the course. In: Gattaz WF, Häfner H, editors. Search for the causes of schizophrenia. 4. Balance of the century, Darmstadt: Steinkopff; Berlin: Springer. p 38.

Iversson LB. 1974. Aspectos Epidemiológicos da meningite meningoccocica no municipio de São Paulo (Brasil) no período de 1968 a 1974. Rev Saude publ S. Paulo 10:1–16.

Janca A, Hiller W. 1996. ICD-10 Checklists – A tool for clinicians. Use of the ICD-10 Classification of Mental and Behavioral Disorders. Compr Psychiatry 37(3):180–187.

Menninger KA. 1928. The schizophrenic syndromes as a product of acute infectious disease. Arch Neurol Psychiatry 20:464–481.

Leask SJ, Done J, Crow TJ. 2002. Adult Psychosis, common childhood infections and neurological soft signs in a national bith cohort. Br J Psychiatry 181:387–392.

Lim KO, Beal DM, Harvey RL Jr, Myers T, Lane B, Sullivan EV, Faustman WO, Pfefferbaum A. 1995. Brain dysmorphology in adults with congeniatal rubella plus schizophrenialike symptoms. Soc Biol Psyhciatry 37:764–776.

Rantakallio P, Jones P, Moring J, Von Wendt L. 1997. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: A 28-year follow-up. Int J Epidemiol 26(4):837–843.

Robins LN, Regier DA. 1990. Psychiatric disorders in America – The Epidemiologic Cathment Area Study. New York: The Free Press. pp 329–343.

Wright P, Takei N, Murray RM, Sham PC. 1999. Seasonality, prenatal influenza exposure, and schizophrenia. In: Susser ES, Brown AS, Gorman JM, editors. Prenatal exposures in schizophrenia. Progress in psychiatry series, no. 56. Washington and London: American Psychiatric Press. pp 89–112.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 49–55

LECTURE

Future contributions on genetics

MARIE-ODILE KREBS

Inserm E0117; Université René Descartes, Paris; Hôpital Sainte-Anne, Paris; France

Abstract
It has become obvious from epidemiological studies in families of patients affected or from twin studies, that most psychiatric disorders are in part genetically determined. Genetics have raised incredible hopes that the complex nature of psychiatric disorders might be unravelled. However, progress in psychiatry genetics have met major difficulties that have hampered psychiatry taking advantage of the new technologies as compared to other fields, such as neurology. In this non-exhaustive review, we propose an overview from the initial evidence to the expected future, through a critical statement on the current situation.

Key words: *Bipolar, schizophrenia, candidate gene, epigenetic, endophenotype*

Where we started: The evidences

The work of the monk Georges Mendel is often quoted as a reference in genetics. He proposed the idea that physical qualitative characteristics (in peas) are determined by inherited factors in a simple manner with either recessive or dominant transmission (reviewed in Gershon 2000). A 'simple' transposition to human disease has led to the concept that physical diseases (or characteristics) can be determined by inherited factors.

Based on this Mendelian model, linkage studies have been conducted, which examine whether the transmission of the disease coincides with that of a genetic marker that, in turn, allows to compute the probability that a marker gene and the disease gene co-segregate, thus giving information on the location of the disease gene. This requires the knowledge of the mode of inheritance, and the allele frequencies in the general population. It also postulates that the disease's penetrance is complete or almost complete to ensure that the clinical status 'affected' or 'non affected' is sufficiently reliable. Indeed, false attribution of the clinical status would bias the results (Tsuang 1999).

The reality in psychiatry is different (Sawa and Snyder 2002; Kennedy 2003). Firstly, although familial aggregation has been demonstrated for the main psychiatric disorders, the mode of inheritance is still unknown. Some family studies support a dominant transmission, other a 'recessive' transmission. There is also suggestion that some forms of psychiatric disorders (including schizophrenia or autism) are X-linked diseases, or with an excess of maternal transmssion that could be compatible with mitochondrial transmission.

Secondly, the penetrance is obviously incomplete, leading to attenuated forms of diseases or to related disease in the 'spectrum'. When those attenuated forms are present in the relatives of the patients, this can lead to false 'unaffected' status and bias the result of linkage studies. The influence of other factors from the environment or of other genetic modulators is highly suspected in diseases such as schizophrenia, bipolar or anxiety disorders (Tsuang 2000).

Thirdly, there is evidence of pleiotropism: the same genetic variation can express in different manners, leading to different phenotypes and diagnosis, challenging the nosographic classification (Ozaki et al. 2003).

Lastly, in line with other complex diseases, there is also evidence of a genetic heterogeneity (Gershon 2000). Given the high frequency of the genetic variants concerned and non-Mendelian phenomena such as associative mating, the probability of the involvement of different variants on different genes is high, even within the same family.

Correspondence: Dr Marie-Odile Krebs, Inserm E 0117-Paris V, Service Hospitalo Universitaire, Hôpital Sainte Anne, 7 Rue Cabanis, 75014 Paris, France. E-mail: krebs@broca.inserm.fr

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030072

Despite all these limitations, the Mendelian model has been promoted in genetic studies in psychiatry, perhaps because of the progress in the discovery of causative genes for single-gene diseases, including in neurology.

However, there are other founding models that could be more adapted to the field of psychiatry (see Gershon et al. 2000). Back in 1865, Galton proposed the model of heritability, suggesting that quantitative traits are correlated between individuals of the same family. In 1918, Fisher introduced the notion of polygenic inheritance, suggesting that the correlation of qualitative traits in related individuals could be modelled as the sum of effects of a large number of genes, with additive effects, albeit having individually minor effects. It has been subsequently shown that a few genes (two to four), each having a small contribution to relative risk, would best fit the model of transmission in schizophrenia or bipolar disorders (Risch 1990).

In this regard, psychiatric disorders are closer to other complex and frequent disorders like diabetes or asthma than to neurological conditions such as Parkinson's or Huntington's diseases.

In diabetes and asthma, genome scan studies gave results similar to those in psychiatric disorders, identifying few regions with highly significant evidence of linkage and few replications in multiple independent studies. As underlined by Gershon (2000), if a disease is common and results from several genes, it follows that the genes are much more common than the disease. The use of incorrect assumptions in the early analysis of bipolar pedigree led to rejection of the linkage when new cases appeared that did not carry the suspected gene variants. In this situation, an oligogenic model would have given a different conclusion, assuming that new cases could result from other common genes being brought into the pedigree by persons marrying in (Badner et al. 1998).

The initial hypothesis has now been fully demonstrated: 'mental' disorders (or psychiatric diseases) are related to genetic predisposition. Epidemiological studies as well twin studies have indeed largely confirmed that the overall lifetime relative risk of having a psychiatric disorder is higher in the relatives of psychiatric patients than in the general population. The relative risks rapidly decrease as the link with the proband is weaker: ranging from 46 to 48% for monozygotic twins or children of two parents with schizophrenia to 10% for siblings, 5% for grandchildren and 2% for cousins. The estimated shared genes are in comparison ranging from 100 to 50, 25 and 12.5%, respectively (Gottesman, 1997; reviewed in Tsuang 2000).

But in a family, much more than genes are shared. It has become increasingly obvious that genetic factors do not account for the whole determinism of psychiatric disorders, and that the so-called 'environment' also plays a major role (Tsuang 2000). The role of genes has nevertheless been confirmed by adoption studies, showing that 'the biological offspring of a parent with schizophrenia develop the disease at the rate of their biological origins not of their adoptive environment' (Ingraham and Kety 2000). The relative contribution of genes and environment can be partitioned based on population genetics and twin studies. The phenotypic variance V_p represents the addition of the genetic variance (V_g, or heritability) + the environmental variance (V_e) + the residual variance (V_{error}). This can be further detailed in $V_p = (V_{g\ additive} + V_{g\ dominance} + V_{g\ epistatic}) + (V_{e\ common} + V_{e\ unshared} + V_{g \times e}) + V_{error}$. Structural equations modelling of populations has determined the contributions to the liability for the disease of additive and dominance genetic, and the shared and unique environmental factors (see Tsuang 2000).

In line with the dominant 'Mendelian' model, numerous linkage studies have been performed using 'parametric' analysis in large pedigrees, although the oligogenic model would have predicted that studies in numerous smaller families are more reliable. In addition, early studies have focussed their phenotypic determination on diagnostic categorization, done with interviews, compared to multiple anonymous DNA markers genotyped from DNA of leucocytes taken in peripheral samples. In schizophrenia and bipolar disorder, this classical strategy has lead to the identification of numerous regions that could confer higher liability to the diseases. Some of them have been replicated (i.e. 1p21, 1q32–41; 2p22–q21; 3p26–24, 4q24–q32; 5q11–13, 6q21, 6p22–24, 7q22, 8p21–22, 8q12, 9q34, 10p; 11q; 13q 32, 15q13–14; 22q11,X), but always with discordant studies as well (Pulver, 2000; Lewis 2003, Harrison and Owen 2004; Shirts and Nimgaonkar 2004; Levinson et al 2005). Among those regions, the most consistent appear to be: 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q, and 14p (Lewis et al. 2003). Increasing the complexity further, some regions appear to be common between schizophrenia and bipolar disorders (Badner and Gershon 2002; Segurado et al. 2003; McGregor 2004) and in particular, 13q and 22q.

Where are we? Are we progressing?

Several comprehensive reviews have been published recently stating the current findings in psychiatry genetics (Harrison and Owen 2004; Owen and

Williams 2004; Shirts and Nimgaonkar 2004), and especially in schizophrenia and bipolar disorders, to which the readers are recommended to refer. In this paper we wish to draw a more general overview on this domain of knowledge and how progress has been made and which strategies are now favoured.

Since the pioneer studies in the late 1970s, there have been extensive fundings supporting extensive studies in schizophrenia and bipolar disorders. As already underlined, the classical strategy of linkage analysis in large pedigrees has been largely promoted. In the mean time, the biotechnology revolution has brought in 'high throughput' technologies allowing us to genotype increasing numbers of markers in decreasing times. By chance, concomitantly, the human genome project has identified multiple markers: in particular, hundreds of thousands of single nucleotide polymorphisms have been identified through the genome and have joined repeated sequences, micro-satellites as markers of genetic variations (Neale and Sham 2004).

Despite these advances, the overall resigned conclusion is usually that all those efforts are 'less than conclusive' (Tsuang 2000). New hopes have emerged in the last 2 years because of convergent findings and/or replications (Harrison and Owen 2003; Kennedy 2003; Harrison and Weinberger 2005).

The general impression is that of an 'up and down progression' where psychiatric genetics, by a strange empathy, mimics the object of observation, i.e. bipolar disorders! This progression can be caricatured as: phases of 'over-enthusiasm' alternating with phases of 'over-pessimism', with a partial time-correlation with publications of determinant advances by geneticists, followed by adjustments to 'psychiatric reality'. This can be illustrated by the following.

Linkage studies

One of the most conclusive results, contrasting with the reports of 'almost' significant linkage, was the report on the linkage of schizophrenia with markers in the 1q region with a LOD score of 6.5 (Brzustowicz et al. 2000). Before and since then, however, several large scale trials were not able to find any linkage in that region, which was finally reported as a liability region by some but not all recent analyses (Levinson et al. 2002), despite the region encompasses the region of the gene DISC1, independently demonstrated as being involved in schizophenia (Millar et al. 2004).

Chromosomal abnormalities

The association of a micro-deletion in q11 region of chromosome 22 with a higher risk of schizophrenia or bipolar disorder is another major finding (see Murphy 2002 for review). This microdeletion, also responsible for velo-cardio-facial syndrome, was one the first pieces of direct evidence of chromosomal abnormalities related to major psychosis. Nevertheless, attempts to identify the gene(s) responsible for the psychiatric syndrome have been rather inconclusive. Linkage studies have brought both supportive and discrepant results, with some papers excluding the 22q11 region in schizophrenia (Mowry et al. 2004). Several genes of interest are located within or near the deleted region, including COMT (catechol-*O*-methyltransferase, a degrading enzyme for dopamine) and proline deshydrogenase (ProDH, a mitochondrial enzyme). Nevertheless, hyperprolinemia is not always associated with schizophrenia and, conversely, psychiatric syndromes are not always associated with hyperprolinemia, even within the pedigree carrying the mutation (Jacquet et al. 2002). Moreover, a recent study in a large sample, reported a negative association with ProDH polymorphism (Williams et al. 2003). Association studies exploring COMT as candidate gene in schizophrenia and bipolar disorders, led to overall negative results (Mufado et al. 2005). Nevertheless, COMT gene variants could influence cognitive functions in relation to the prefrontal cortex (Egan et al. 2001; Goldberg et al. 2003).

Candidate genes

In an different approach than genome wide screening, association studies have looked at genes that are 'candidate' because of their position in the genome in the region of interest, identified in chromosomal abnormalities or by linkage studies ('positional candidate genes'; e.g., COMT, COMT, DISC1, neuregulin 1, G72) or because of their involvement in neurotransmission or function ('functional candidate genes', e.g., dopamine receptor type 3, DRD3, 5HT2 receptor, brain-derived neurotrophic factor BDNF, etc.). For each candidate, numerous positive and negative reports have been compelling. Meta-analysis sometimes supports a weak association (e.g., DRD3 in schizophrenia, Jonsson et al. 2003). Even the widely replicated result concerning neuregulin (NR1) (Stefansson et al. 2004; Petryshan and Middleton 2005) was not always replicated (Thiselton et al. 2004), even though the sample was large enough. Another intriguing feature is the increasing number of studies reporting positive results in bipolar disorder using gene variants candidate for schizophrenia and reciprocally.

This historical view, not contradicted by recent reports, results in reinforcing the surrounding scepticism: 'are we progressing at all?' In a more 'positive attitude', these observations prompt us to address some questions on the diseases, genetics, and the way we are studying them. Firstly, do we know how relevant the phenotypes are? For example, the so-called 'schizophrenia spectrum', resulting from aggregation studies, actually encompasses a large variety of disorders: schizophrenia; schizo-affectifve disorder; schizophreniform disorder; delusional disorders; atypical psychosis; psychosis NOS; bipolar disorder; unipolar disorder; cluster A personality disorders, avoiding personality; anxiety disorder; alcoolism, substance abuse disorder, etc. In other words, we should not count on phenotypic homogeneity in the family. In addition, the penetrance is obviously not complete and presumed carriers are not always affected. However, presumed carriers, could display some characteristics associated with the disease called 'endophenotypes', 'intermediate phenotypes' or 'vulnerability markers' (Gottesman and Gould 2003). Numerous cognitive neurophysiological (Freedman et al. 1999) or even simpler neurological (Gourion et al. 2004) characteristics were described associated with schizophrenia and found at a higher prevalence in relatives of patients than in the general population.

Pleiotropic effect has been recently stressed by a report on two families with serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype encompassing OCD, depression, Asperger syndrome, tics, alcohol, anxiety (PTSD, phobias) and anorexia nervosa (Ozaki et al. 2003)! In addition, genetic variations in MECP2 were found associated with mental retardation, autisms, and Asperger syndrome (see Zoghbi 2003; Veenstra-WanderWeele and Cook 2004).

Secondly, how many genetic factors are we looking for in the different diseases? Recent meta-analysis of linkage studies supports the idea that genes located in the 13q and 22q regions are involved in the pathophysiology of both schizophrenia and bipolar disorder. On the other hand, the effect of each individual gene could be minor.

The intermediate and not comforting conclusion is that there is no simple phenotype–genotype concordance. Besides the phenotypic issues, we need to take into account: (i) gene × gene interactions (that could be additive, negative, epistatic or multiplicative); (ii) environment factors; (iii) gene × environment interactions. These different interactions could modulate the expression of genetic variations and, in turn, hamper the identification of genes involved in psychiatric diseases.

New strategies and new pitfalls

In response to these analyses, new strategies and recommendations were defined for future genetic studies.

1. 'More': the first strategy to avoid false-positives was to encourage studies on larger samples of subjects and to replicate the finding in more populations, preferentially in a different ethnic genetic background. In addition, the use of more polymorphisms in the same gene was recommended in order to work on haplotype rather than on individual markers, less likely to have functional relevance unless this has been independently proved (e.g., non-synonymous mutation in the coding part of the gene). Regarding statistics, by contrast with classical linkage studies, non-parametric studies were preferred (e.g., sib-pairs studies) as well as intra-familial association studies (transmission disequilibrium test), that minimize the risk of stratification bias compared to population-based association studies. Yet, those strategies raise the question that large populations might have less homogeneous origins and/or could hamper the identification of rare familial forms. In addition, although statistics on larger numbers are more reliable, they remain informative rather than demonstrative, since they give no pathophysiological explanations.
2. Numerous studies have directly addressed the question of the clinical definition with the use of endophenotypes or intermediate phenotypes. Three papers are emblematic in this regard. Using P50 modulation in schizophrenia, Freedman et al. (1997) provided the earliest demonstration in psychiatry that neurophysiological characteristics could be more informative that diagnosis. Indeed, while they did not find a linkage with schizophrenia using a marker located in chromosome 15 (location of α7 nicotinic receptor), there was a significant linkage when the ratio of P50 amplitudes was used to qualify the clinical status of the subjects (whether or not affected). Using a functional gene variant of COMT (Val108/158Met) that modulates the level of dopamine, Egan et al. found an association with performance in the Wisconsin Card Sorting Test, reflecting prefrontal function (2001). This was true in patients with schizophrenia, their relatives but also in 'normal' controls. Lastly, exploring a functional variant in the BDNF gene (Val66Met), homozygous subjects for the 'Met' allele displayed poorer episodic memory and abnormal hippocampal activation, while

there was no association with schizophrenia (Egan et al. 2003).

These results are particularly informative because they give 'sense' to the genetic findings through the functional consequences. Nevertheless, the question remains whether they are really related to the diseases or whether they are modifier genes that confer specific characteristics, whatever the disease or the status (affected or not). In line with that, there is compelling evidence that BDNF could be associated with age at onset in various neuropsychiatric diseases (Krebs et al. 2000; Kunugi et al. 2001; Millet et al. 2002; Ribases et al. 2004) or that the polymorphism of the serotonin transporter 5HTTLPR is associated with violent behaviour in different conditions (Hallikainen et al. 1999; Bondy et al. 2000; Courtet et al. 2001; Bayle et al. 2003).

3. More recently, together with the advances of biotechnologies, emphasis was given to convergent strategies.

   Not only should genetic studies consider chromosomal approaches, linkage and candidate gene strategies together with relevant phenotypes, but they should be replaced in the context of knowledge stemming from post-mortem and micro-array studies, animal models, and any evidence for functional consequence of the genetic variation (e.g., modification in the expression of peripheral factors or functional brain imaging). Indeed, recent findings in genetics make sense because they are consistent with neurobiological studies and with post-mortem studies (reviewed in Harrison and Weinberger 2004; Harrison and Owen 2003). In line with this, neuregulin (NRG1), dysbindin (DTNBPI), G72, DAAO, RGS4, COMT, and PRODH can all be integrated with regard to their function in the glutamatergic synapse and, thus, join the glutamatergic hypothesis of schizophrenia. On the other hand, MECP2 (methyl-CpG-binding domain) and neuroligins, involved in Rett syndrome, autism and related disorders, could involved in synapse modulation or maintenance (Zhoghbi 2003).

   This strategy implies either to reconstruct the model on the basis of the identified genes, or to direct the genetic studies based on functional studies. The risk is then to miss unexpected candidates or to miss human-specific regulation while working in animal model.

4. As stressed above, gene are not isolated in the aetiology of psychiatric disorders and the gene × environment interaction should be considered (Tsuang 2000). This implies to use both genetics and epidemiology. For example, 5HTT gene variants appear to modulate the influence of life stress on depression (Caspi et al. 2003). These kinds of approach are the subject of numerous biases that should be carefully examined (population bias, recruitment bias, follow up bias, etc.). They bring, however, new and meaningful results on individual vulnerability to the environment.

Where do we go?

The overall evaluation of the current situation should not be pessimistic. Some genes have undoubtedly been identified, which are involved in schizophrenia, anorexia, autism, etc. In addition, there is compelling evidence underscoring the role of common dysfunctional pathways in several major psychiatric disorders 'meeting at the synapse' and making the neuronal and/or synapse plasticity as the core of the problem (Harrison and Owen 2003; Zoghbi 2003).

In the future, we will need to differentiate the genes in relation with what they are responsible for: vulnerability to overall mental disorders? specific vulnerability? progression of the disease? This implies, in particular, to identify the genes that differentiate the patients from their unaffected siblings and the processes by which they interact with early or late environment to trigger disease progression. This could lead in turn to new therapeutic as well as preventive strategies.

Genetic has provided new dreams about the complexity and superiority of Mankind, in relation to the complexity of the central nervous system. Yet, with only 25,000 genes, our genome is far more restricted than initially thought and, actually, not very different from the ancestral genome of the worm *C. elegans*. Partially compensating this relative deficit, most genes are expressed in the brain.

However, there is increasing evidence that everything is not directly in the code. There are other levels of regulation that should not be forgotten (Strohman 2002). Firstly, genes are included in a protein complex that influences the accessibility of the genome, for example, for the enzymes responsible for transcription, duplication, etc. Secondly, the functional state of a segment of chromosome is determined by acetylation, methylation, phosphorylation, ubiquitination and ribosylation of the amino acids of the histone tails. Lastly, the DNA sequence itself can be modified by cytosine methylation.

From genotype to phenotype, the levels of regulation also include epigenetic regulation of gene expression, post-translational modification

of proteins, metabolic networks of glycosis and mitochondrial oxidation–reduction (Strohman 2002).

Epigenetic regulation (and in particular methylation) is in particular underscored as an important key in the genetics of psychiatric disorders (Pantelis 2003; Abdolmaleky et al. 2004). Epigenetic metastability might shed light on various non-Mendelian irregularities and help address a series of issues that cannot be explained by traditional genetics. Monozygotic twins discordance might be due to differential epigenetic modification between the twins. Parent of origin transmission could be related to transmission of specific modifications of DNA and histones. The effect of the environment might be via modification of the epigenetic status. The gender difference could be related to differential effects of androgens and estrogens on epigenetic regulations. The phenotypic variability over time could result from the changes induced by environment and developmental events. Lastly, remission and relapse fluctuations can be related to age- or treatment-related epigenetic changes.

In conclusion, we should be aware that genetics alone will not solve the problems of the aetiological origin of psychiatric disorders, yet we need genetics to understand the pathophysiology of psychiatric diseases. This underscores the need for more integrated genetics with adapted phenotypic, biological and brain imaging strategy. While we are still in the 'genome era', we shall already turn towards the post-genome era that might help us to understand inconsistency of classical genetic models.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ, et al. 2004. Methylomics in psychiatry: Modulation of gene-environment interactions may be through DNA methylation. Am J Med Genet B Neuropsychiatr Genet 127(1):51–59.

Badner JA, Gershon ES, Goldin LR. 1998. Optimal ascertainment strategies to detect linkage to common disease alleles. Am J Hum Genet 63(3):880–888.

Badner JA, Gershon ES. 2002. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 7(4):405–411.

Bayle FJ, Leroy S, Gourion D, Millet B, Olié JP, Poirier MF, Krebs MO. 2003. 5HTTLPR polymorphism in schizophrenic patients: further support for association with violent suicide attempts. Am J Med Genet 119B:13–17.

Bellivier F, Szoke A, Henry C, Lacoste J, Bottos C, Nosten-Bertrand M. 2000. Possible association between serotonin transporter gene polymorphism and violent suicidal behavior in mood disorders. Biol Psychiatry 48:319–322.

Bondy B, Erfurth A, de Jonge S, Kruger M, Meyer H. 2000. Possible association of the short allele of the serotonin transporter promoter gene polymorphism (5-HTTLPR) with violent suicide. Mol Psychiatry 5:193–195.

Brzustowicz LM, Hodgkinson KA, Chow EW, Honer WG, Bassett AS. 2000. Location of a major susceptibility locus for familial schizophrenia onchromosome 1q21–q22. Science 28; 288(5466):678–682.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H. 2003. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 301(5631):386–389.

Courtet P, Baud P, Abbar M, Boulenger JP, Castelnau D, Mouthon D, Malafosse A, Buresi C. 2001. Association between violent suicidal behavior and the low activity allele of the serotonin transporter gene. Mol Psychiatry 6(3):338–341.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 5;98(12): 6917–6922.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269.

Evans DM, Cardon LR, Morris AP. 2004. Genotype prediction using a dense map of SNPs. Genet Epidemiol 27(4):375–384.

Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al. 1997. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci USA 21;94(2):587–592.

Freedman R, Adler LE, Leonard S. 1999. Alternative phenotypes for the complex genetics of schizophrenia. Biol Psychiatry 1;45(5):551–558.

Gershon ES. 2000. Bipolar illness and schizophrenia as oligogenic diseases: Implications for the future. Biol Psychiatry 1;47(3): 240–244.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS. 2003. Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158-Met genotype and schizophrenia. Arch Gen Psychiatry 60(9):889–896.

Gottesman II, Gould TD. 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. Am J Psychiatry 160(4):636–645.

Gottesman II, Moldin SO. 1997. Schizophrenia genetics at the millennium: Cautious optimism. Clin Genet 52(5):404–407.

Gourion D, Goldberger C, Olie JP, Krebs MO. 2004. Subtle neurological and morphological anomalies in presumed-carriers of the genetic liability to schizophrenia. Schizophr Res 67:23–31.

Harrison PJ, Owen MJ. 2003. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 361(9355):417–419.

Harrison PJ, Weinberger DR. 2005. Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. Mol Psychiatry 10(4):420.

Ingraham LJ, Kety SS. 2000. Adoption studies of schizophrenia. Am J Med Genet 97(1):18–22.

Jacquet H, Raux G, Thibaut F, Hecketsweiler B, Houy E, Demilly C, et al. 2002. PRODH mutations and hyperprolinemia in a subset of schizophrenic patients. Hum Mol Genet 11(19):2243–2249.

Jonsson EG, Flyckt L, Burgert E, Crocq MA, Forslund K, Mattila-Evenden M. 2003. Dopamine D3 receptor gene

Ser9Gly variant and schizophrenia: association study and meta-analysis Psychiatry Genet 13:1–12.

Kennedy JL, Farrer LA, Andreasen NC, Mayeux R, St George-Hyslop P. 2003. The genetics of adult-onset neuropsychiatric disease: Complexities and conundra? Science 302(5646):822–826.

Krebs MO, Guillin O, Bourdell MC, Schwartz JC, Olié JP, Poirier MF. 2000. Brain derived neurotrophic factor (BDNF) gene variants association with age at onset and therapeutic response in schizophrenia. Mol Psychiatry 5:558–562.

Kunugi H, Ueki A, Otsuka M, Isse K, Hirasawa H, Kato N. 2001. A novel polymorphism of the brain-derived neurotroph ic factor (BDNF) gene associated with late-onset Alzheimer's disease. Mol Psychiatry 6:83–86.

Levinson DF. 2005. Meta-analysis in psychiatric genetics. Curr Psychiatry Rep 7(2):143–151.

Levinson DF, Holmans PA, Laurent C, Riley B, Pulver AE, Gejman PV. 2002. No major schizophrenia locus detected on chromosome 1q in a large multicenter sample. Science 296 (5568):739–741.

Levinson DF, Levinson MD, Segurado R, Lewis CM. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part I: Methods and power analysis. Am J Hum Genet 73(1):17–33.

Levinson DF, Levinson MD, Seguardo R, Lewis CM. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet 73(1):34–48.

Levy DL, O'Driscoll G, Matthysse S, Cook SR, Holzman PS, Mendell NR. 2004. Antisaccade performance in biological relatives of schizophrenia patients: A meta-analysis. Schizophr Res 71(1):113–125.

Macgregor S, Visscher PM, Knott SA, Thomson P, Porteous DJ, Millar JK, et al. 2004. A genome scan and follow-up study identify a bipolar disorder susceptibility locus on chromosome 1q42. Mol Psychiatry 9(12):1083–1090.

Millar JK, James R, Brandon NJ, Thomson PA. 2004. DISC1 and DISC2: Discovering and dissecting molecular mechanisms underlying psychiatric illness. Ann Med 36(5):367–378.

Millet B, Chabanne N, Delorme R, Leboyer M, Leroy S, Bourdel MC. 2002. A trend for an association between BDNF gene and obsessive compulsive disorder. Am J Med Genet 114:838–839.

Mowry BJ, Holmans PA, Pulver AE, Gejman PV, Riley B, Williams NM. 2004. Multicenter linkage study of schizophrenia loci on chromosome 22q. Mol Psychiatry 9(8):784–795.

Munafo MR, Bowes L, Clark TG, Flint J. 2005. Lack of association of the COMT (Val(158/108) Met) gene and schizophrenia: a meta-analysis of case-control studies. Mol Psychiatry in press.

Murphy KC. 2002. Schizophrenia and velo-cardio-facial syndrome. Lancet 359(9304):426–430.

Neale BM, Sham PC. 2004. The future of association studies: Gene-based analysis and replication. Am J Hum Genet 75(3):353–362.

Owen MJ, Williams NM, O'Donovan MC. 2004. The molecular genetics of schizophrenia: New findings promise new insights. Mol Psychiatry 9(1):14–27.

Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, et al. 2003. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. Mol Psychiatry 8(11):895, 933–936.

Petronis A. 2004. The origin of schizophrenia: Genetic thesis, epigenetic antithesis, and resolving synthesis. Biol Psychiatry 55(10):965–970.

Petryshen TL, Middleton FA, Kirby A, Aldinger KA, Purcell S, Tahl AR, et al. 2005. Support for involvement of neuregulin 1 in schizophrenia pathophysiology. Mol Psychiatry 10(4):366–374, 328.

Pulver AE. 2000. Search for schizophrenia susceptibility genes. Biol Psychiatry 47(3):221–230.

Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, Anderluh M. 2004. Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations. Hum Mol Genet 13:1205–1212.

Risch N. 1990. Linkage strategies for genetically complex traits. III. The effect of marke polymorphism on analysis of affected relative pairs. Am J Hum Genet 46(2):242–253.

Sawa A, Snyder SH. 2002. Schizophrenia: Diverse approaches to a complex disease. Science 296(5568):692–695.

Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI Jr, et al. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. Am J Hum Genet 73(1):49–62.

Shirts BH, Nimgaonkar V. 2004. The genes for schizophrenia: finally a breakthrough? Curr Psychiatry Rep 6(4):303–312.

Stefansson H, Steinthorsdottir V, Thorgeirsson TE, Gulcher JR, Stefansson K. 2004. Neuregulin 1 and schizophrenia. Ann Med 36(1):62–71.

Strohman R. 2002. Maneuvering in the complex path from genotype to phenotype. Science 296(5568):701–703.

Thiselton DL, Webb BT, Neale BM, Ribble RC, O'Neill FA, Wash D, et al. 2004. No evidence for linkage or association of neuregulin-1 (NRG1) with disease in the Irish study of high-density schizophrenia families (ISHDSF). Mol Psychiatry 9(8):777–783; image 729.

Tiihonen J, Hallikainen T, Lachman H, Saito T, Volavka J, Kauhanen J, et al. 1999. Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry 4:385–388.

Tsuang M. 2000. Schizophrenia: genes and environment. Biol Psychiatry 47(3):210–220.

Tsuang MT, Stone WS, Faraone SV. 1999. Schizophrenia: A review of genetic studies. Harv Rev Psychiatry 7(4):185–207.

Veenstra-VanderWeele J, Cook EH Jr. 2004. Molecular genetics of autism spectrum disorder. Mol Psychiatry 9(9):819–832.

Williams NM, Owen MJ. 2004. Genetic abnormalities of chromosome 22 and the development of psychosis. Curr Psychiatry Rep 6(3):176–182.

Zoghbi HY. 2003. Postnatal neurodevelopmental disorders: Meeting at the synapse? Science 302(5646):826–830.

The World Journal of Biological Psychiatry, 2005; 6(Suppl 2): 56–64

LECTURE

Forthcoming ethical issues in biological psychiatry

HANFRIED HELMCHEN

Department of Psychiatry and Psychotherapy, Charité – University Medicine of Berlin, Free University, Germany

Abstract
Ethical issues in biological psychiatry are framed by (i) progress in the neurosciences, and (ii) a changing socio-cultural context. With regard to forthcoming *neurotechniques* to modify specifically defined brain functions by pharmacological substances with selective effects, by activating neuroplasticity including neurogenesis, or by implantation of neuronal tissues or computer–brain interfaces, etc., ethical problems will develop (i) at the border between therapy of diseases and enhancement of abilities in healthy people with regard to effects on society (e.g., social justice: equal access, loss of societal diversity) as well as on human value systems (e.g., personality, efforts, conditio humana), and (ii) at the border between the medical system and the wellness market with regard to financing what by whom? Ethical *dilemmas* in psychiatry develop (i) between the individual's best and the common good (demanded from *outside* medicine), (ii) among different ethical principles (*inside* medicine), iii) if solutions are influenced by personal reasons without observing ethical principles. Ethical *guidelines* are necessary for ethical orientation, but may protect against misconduct only (i) if psychiatrists are educated in ethics and (ii) if psychiatric acting is under continuous debate (by ethical review boards or the public). Thus, if we psychiatrists will become ethically sensitive by reflecting and perhaps solving our *current* ethical dilemmas we will be prepared to deal with *forthcoming* ethical issues in biological psychiatry.

Key words: *Ethical dilemmas, clinical research, neurotechniques, genetic prediction, enhancement*

Prologue

Forthcoming ethical issues in biological psychiatry are, first, unsolved ethical problems of our time and, second, ethical problems which may be expected in the future due both to progress in the *neurosciences* and to changes of the *social context* of psychiatry.

Psychiatric ethics can be seen as the application of general ethical norms to psychiatric dealings with psychically ill persons. Thus, the prevailing moral principles in a *society*, as well as their change, will influence the recognition and solution of ethical problems in psychiatry. Their differentiated recognition may be increased by growing sensitivity, but generally accepted solutions become more and more difficult in increasingly multicultural societies where a generally binding value system no longer seems to exist.

Forthcoming ethical issues in biological psychiatry will be caused by the progress of the *neurosciences*. Biological psychiatry deals with neuroscientific gain of knowledge by research with patients, as well as with the application of neuroscientific knowledge in the diagnosis and treatment of patients with brain diseases or functional brain disturbances. There is a considerable research demand for these disorders, due to their high frequency, long duration, disabling consequences, and unsatisfactory or non-existent treatment possibilities. Such indispensable research with patients implies the basic ethical problem of tension between respect of autonomy and the best interest of the ill individual and the likewise ethically justified demand for scientifically flawless research in recognition, prevention, elimination, or attenuation of disability and suffering determined by disease. Demand for research nowadays also results from an increasing orientation of insurance companies towards scientifically proven evidence of the efficacy and safety of medical interventions: 'evidence-based medicine'. The increasing potential to modify specifically the brain functions and thus possibly the self of human beings will result in new ethical problems in the future, e.g., those which are related to the separation of therapy from enhancement.

Correspondence: Hanfried Helmchen, Charité – University Medicine Berlin, Department of Psychiatry, Eschenallee 3, 14 050 Berlin, Germany. E-mail: hanfried.helmchen@charite.de

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970510030081

Let us briefly consider contemporary (III) and future (IV) major ethical issues in biological psychiatry between a changing socio-cultural context (I) and progress in the neurosciences (II).

I. Socio-cultural context of psychiatry

The socio-cultural context of psychiatry exerts its influence not only on the awareness of ethical problems, but also creates most of them, particularly by a variety of dynamic forces driving the development of psychiatry. To name only three:

Public attitudes

Public attitudes have a strong impact on psychiatric practice and research as well. The growing recognition of human and civil rights, of the concepts of human dignity, autonomy and freedom, have made the care of and research with psychiatric patients more humane, but also in some sense more difficult and more bureaucratic. The cornerstone of this development is the legal concept of *informed consent*. This requires specific attention in psychiatry because all major psychiatric diseases may impair the capacity to consent. Some exaggerations, such as the denial of psychiatric diseases and accusations of psychiatric misconduct by the antipsychiatric movement of the past decades, activated much distrust among the public and patients against psychiatry, especially its biological orientation, which hampered psychiatric research: young psychiatrists turned their backs on biological research or even on any clinical research in psychiatry; and recruitment of patients became a cumbersome enterprise. However, the public as well as the professional sensibility towards ethical problems in psychiatry has increased considerably. These attitudes, of course, had and have an impact on politics and legal actions for special laws and administrative directives.

To be more specific: continuously recognized and discussed in public is the ethical question of *justice*, i.e. a fair distribution of benefits and risks, especially in the relationship between the individual's best interest and the common good. The answers given depend upon the public attitudes towards the values of individual freedom and autonomy versus the values of community and solidarity.

Economical and financial consequences of social crises

Economical and financial consequences of social crises, e.g., after World War I in Germany or nowadays world-wide due to the current critical transition of social systems, exaggerate negative public attitudes against the mentally ill and the financing of their care. Financial restrictions and their consequences increasingly impair medical decisions in practice and research.

1. Thus, e.g., a fixed budget for the prescription of drugs places the psychiatrist in practice between two risks: to use a cheap neuroleptic with the risk of *tardive dyskinesia* (for which he may be held liable), or to prescribe an expensive antipsychotic drug without the potential of tardive dyskinesia but with the risk of being taken into recourse by an insurance company.
2. In *research* (and medical education) an upward tendency of sponsoring can be observed. Such co-operation between industry (or even governments) and psychiatrists is needed, because psychiatrists have the patients and the experience with the clinical effects of drugs and the industry has the financial means for research which are needed due to its enormous costs and also to the cutting of public financing. However, this co-operation may also impair the *independence* of psychiatrists' decisions towards the individual patient as well as that of his judgement both in clinical practice and in research (WFSBP 2004).

Demographics

Demographic changes with rapidly increasing life expectancy and growth of the old segment of the population raises the frequency of diseases associated with old age, specifically neurodegenerative diseases, e.g., Alzheimer dementia. Dealing with these patients who frequently have lost the competency to consent raises ethical questions with regard to:

1. *care*, e.g., counselling (about what, when, to whom, how?) and substituted decision making (the validity of advance directives?), and
2. *research* because such research without informed consent, the basic requirement for all research with human beings, is legally not admissible in most countries and is ethically considered highly questionable.

II. Scientific progress

The other source of possibly forthcoming ethical problems in biological psychiatry is the progress of the neurosciences. It is driven by the demand of the public for better medicine and the desire of physicians to improve their capacity to help as well as by the curiosity of researchers – and today more than ever by the social mechanisms of modern science. To name only two examples:

1. The increasing rigor of *scientific methodology* may impair the *best interest* of research patients by burdening them not only with inconveniences, e.g., the uncertainties of randomization or blindness in testing, but also with possible disadvantages due to the application of placebo controls.

   Such inconveniencies or disadvantages may be: (i) undermining the trust of patients who wish to receive the individually best treatment and not a therapy by chance (randomization) or by blindness of the doctor (double blind); (ii) incomplete information in order to avoid a high primary drop-out rate with the consequence of recruiting a population with selection bias; (iii) withholding an effective treatment by administering a placebo.
2. *Genetic* knowledge, which may lead to individual risk profiles, is seen as threatening *confidentiality*, particularly toward insurance companies or employers; industrial companies also have a legitimate interest to keep their data confidential in order to protect their knowledge against competing companies (at least until they have the protection of a patent). On the other hand, strong protection of confidentiality may hamper needed epidemiological research (Ward et al. 2004).

III. Unsolved contemporary ethical issues in biological psychiatry

Due to the fact that ethical issues intensely depend on long-lived habits and attitudes in society, some of today's unsolved major ethical problems in psychiatry will continue to occupy psychiatrists into the *near* future. Examples are:

Research with patients unable to give informed consent

There is a *demand for research* with patients lacking the capacity to give informed consent in a variety of medical disciplines including psychiatry. Psychiatric examples are studies needed to improve the treatment of acute manic patients, many of whom are not able to consent, or studies of biological determinants of the progression of Alzheimer's disease as a prerequisite in developing causal treatments.

The *basic ethical problem* is the lack of informed consent to research that may improve the ill condition and by that the impaired or even lost capacity to consent. In such cases research with potentially direct benefit and at most low risks for the incompetent research patient, mainly so-called therapeutic research, is ethically acceptable and legally admissible in most countries if informed consent is substituted by a specific advance directive or a legal guardian. However, this becomes doubtful if such a substitute does not exist or is not possible. Even more, research with incompetent patients is controversial if no immediate benefit for the research patient can be expected. Research with such patients is not permissible according to a deontological position stating that the highly personal right of self-determination in matters of health cannot be assigned to others. On the other hand, a consequentialistic position says that research with incompetent patients may be ethically acceptable if an essential benefit for the group of patients with the included patient's condition or disease can be expected, and if the risk for him is no more than minimal. In the latter case a future task is to establish and implement criteria and procedures for research indications and subject protection under which such research may be ethically acceptable – if at all (Helmchen 2000, 2002).

A prior problem and one to be solved in the immediate future is the *valid assessment* of the capacity to consent. This is ethically relevant because incorrect estimations either lead to an invalid consent and leave the responsibility for decisions with an incompetent patient or else discriminate against a competent patient.

The currently used technique is a rough clinical estimation based on impression. At best it will ask the patient for his understanding of the information on the planned project given to him, i.e. what will be done (aim, procedure, expected benefits and risks), why will it be done, what does it mean for him. The use of standardized tests, such as the McArthur Test Battery (Appelbaum et al. 1995), is time-consuming and its specificity is insufficient (Vollmann et al. 2003, 2004).

Placebo-controlled trials

The methodology of scientific proof of new treatments particularly by randomized and *placebo-controlled clinical trials* as the gold standard has raised unsolved ethical questions, such as informed consent with regard to full information on randomization and blindness, or particularly the recent controversial debate between representatives of a 'placebo orthodoxy' against those of an 'active control orthodoxy'. The core of this debate is the question of whether it is ethically acceptable to withhold an effective treatment in order to have, by means of a placebo control, the best scientific methodology for the proof of the effectiveness of a new treatment. Finally, the ethical problem is the weighing of the individual patients' best interests against the common good; the latter to protect is the duty of the

authorities in licensing only effective and safe treatments for the market.

Research sponsored by industry

Relationships between psychiatrists and the pharmaceutical industry have increased in frequency and intensity, both on the individual level and particularly on the institutional level (Bekelman et al. 2003). They extend from necessary and desirable co-operation through questionable practices to unacceptable misconduct. The problem of an inadmissible influence from industry on the research physician's academic freedom in thinking independently and judging objectively is growing because of an increasing interweaving of industry and medicine, and is aggravated by the present decrease of public financing of academic institutions in many countries.

The following citations call attention to this development: '... profoundly changing relationships with the world of commerce' by an increasing 'transfer of academic scientific discoveries into practice. In so doing it has increased the flow of revenues from patenting and licensing activity into research institutions and their faculties, thereby creating a positive feedback loop that drives the interest of both toward a more vigorous commercialisation of their intellectual property, while arguably creating a new and perhaps dangerous dependency on it. The result has been deepening entanglement of research universities with industry and progressive blurring of the boundaries that once reasonably, albeit not perfectly, demarcated academic interests and values from those of the world of commerce' (Korn 2000). In one article of the *New England Journal of Medicine* (*NEJM*) the editor decided merely to summarise because 'the author's ties with companies that make antidepressant drugs were so intensive that it would have used too much space to disclose them fully' (Angell 2000). In 2000 and 2001, the editors of the *NEJM* could publish only one Drug Therapy article on a novel form of treatment due to the very restrictive requirements for disclosure of financial interests: 'because the essence of reviews and editorials is selection and interpretation of the literature, the *Journal* expects that authors of such articles will not have any financial interest in a company (or its competitor) that makes a product discussed in the article'. This constraint was thought to deprive the readers of the Journal from 'authoritative review articles written ...by the best possible authors', and would make physicians find 'that pharmaceutical companies become their chief source of information about new therapies. Therefore, the editors modified the above cited statement by adding the one word 'significant' between 'any' and 'financial' (Drazen et al. 2002).

The decrease of public financing encourages academic institutions and their employees to apply for sponsorships. However, the developing relationships between academic institutions and industrial companies are a fairly unclear area, a 'totally unexplored terrain' (Korn 2002), with almost no explicit rules for *institutional* relationships to industry (Korn 2000; Shalala 2000). Although the vast majority (89%) of 89 biomedical research institutions receiving the most NIH funding in 1998 at least had a mechanism for disclosure to the institution, 'only 19% had specific prohibitions or limitations of activities related to research or teaching, and 38% had institutional committees to review conflicts of interest' (Cho et al. 2000, cited in DeAngelis 2000). Examples of guidelines are: Association of American Medical Colleges (AAMC) 1990: 'Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research'; Faculty of Medicine Harvard University 1996/2000: 'Faculty Policies on Integrity in Science'; American Society of Gene Therapy (ASGT) 2000 on 'Financial Conflicts of Interest in Clinical Research', or a seminar by NIH 2002 on 'Conflicts of Interest: An Overview for Administrators'.

This is especially relevant for biological psychiatry because major sponsors in psychiatry are drug companies. Recognition of all ethical implications of this growing interweaving of industry and biological psychiatry is a present task which should be solved in the near future in order to implement mechanisms against misconduct. Cases of misconduct have provoked a lively discussion and have initiated recommendations as well as guidelines by psychiatric associations, e.g., the WPA, the RCP, and also this Federation (WFSBP 2004). Their aim is to safeguard the integrity of both psychiatrists and industry and to avoid *endangering the relationship between the physician and the patient*.

An example of an adverse industrial influence on research is *publication bias*. This means mainly underreporting of side-effects or of negative findings. It results in a skewed basis for evaluation of the pros and cons of an intended clinical trial and impairs the balance (equipoise) of expected benefits and risks as a fundamental prerequisite of every trial. This violates Principle 27 of the Declaration of Helsinki ('Negative as well as positive results should be published or otherwise available'), and, worse, the right of the patient to expect that the design of a clinical trial 'has been informed by a scientifically defensible review of what is known already'. Therefore, publication of all results of clinical trials is an obligation of clinical investigators as well as

of funding agencies, not the least because such 'public dissemination recognizes the altruistic motivation of patients who agree to participate'. Accordingly, underreporting of research is deemed to be a form of scientific as well as of ethical misconduct (Chalmers 1990, 2002). The recently published appeal of editors of leading medical journals for complete registration of all clinical trials with full access by the public indicates that this problem and the intrinsic ethical issue has not yet been solved by any means and thus is an ongoing one (De Angelis et al. 2004).

Psychiatric research in developing countries

Research is growing in developing countries. Because at present some of these countries do not have their own research structure, drug trials (including those of psychotropic drugs) mainly will be realized by or are at least under control of companies from the developed world. This and related ethical issues are a growing field as referred to in the recently published review of the Nuffield Council on Bioethics (2002). However, due to shortage of time I can only mention this in passing (see also Macklin 2001).

IV. Forthcoming ethical issues in psychiatry

Based on currently far-reaching developments in science and society, some ethical issues in biological psychiatry can be expected to play a major role in the future. To give some examples:

Genetic prediction of risks

The incredibly fast evolvement of genetics has given evidence that research has to go a long way to discover a molecular genetic basis of psychiatric disorders, because most of them are of polygenic origin, and the understanding of the morbogenic interaction of genes is just in the very early stages. Therefore,

1. the *marketing* of genetic tests for the risk of psychiatric diseases, such as Alzheimer dementia, is not only much too early but ethically more than questionable, because the lay user of such a test either will be insufficiently informed about or cannot process the probabilities of the test result. Even future considerable improvement of such tests will demand sound interpretation of test results by a geneticist or psychiatrist. Even more ethically doubtful is genetic testing for the risk of dementia in sporadic types of dementia as long as there is no clearly effective causal therapy available.
2. More specifically, promises of a so-called individually 'tailored' drug treatment according to the individual genetic profile has been criticized as a 'myth of individualization' (Feuerstein et al. 2003). However, some findings suggest that, in a not so distant future, pharmacogenetics (and pharmacogenomics) may uncover genetic variations that could *predict treatment response*, i.e. outcome and specific side-effects.

   For example, recently a cluster of gene variants conferring susceptibility to tardive dyskinisia (TD) was found which accounted for $>50\%$ of the variance in risk for TD. This resembles the predictive power of cardiac enzymes for detecting myocardial infarction. Accordingly, it would be very helpful for the psychiatrist to have a predictive test for the risk of TD at his disposal in order to protect his patient against this severe and frequent side-effect, by selecting an antipsychotic drug without this potential for a patient at risk. However, the development of such a test is expensive, and industry seems not to be interested in funding such a study (Müller et al. 2004).

   This is also an ethical issue: it should be the responsibility of companies that sell antipsychotic drugs with the potential of inducing TD to reduce this risk in the best possible way. Along the way, the necessary high investment may be paid back by improving a company's image as a responsible one, and, furthermore, by conveying the message to the public that it is not only the drug but its interaction with individual dispositions that must be considered.
3. The case of *Huntington's chorea* demonstrates how psychiatry deals with an increase in knowledge. Today the carrier of the pathogenic gene can be definitely diagnosed presymptomatically. This *predictive testing* raises ethical questions, such as: How will the life of a young member of a Huntington family be influenced by the information that he is a carrier of the gene and will become ill in some years? Or, the other way around: How will the uncertainty burden his life that he, as an offspring of an ill parent, has a 50% risk of contracting the disease? Some members of Huntington families will clear themselves of this uncertainty by the test. Others do not wish to lose, by testing, the hope of not being a carrier. Therefore geneticists, together with psychologists and psychiatrists, have developed rules for counselling members of families concerned.

   Further ethical problems result from the fact that the test can also be *applied to the unborn*. A

positive result will raise the question of abortion. Many parents refuse abortion, hoping for three or four decades of a healthy life for their child; particularly the handicapped refuse abortion on the grounds that they understand such a consequence of the test as negative eugenics, and experience it as a potential threat against their own existence, and as discrimination. Taken the other way around, the delivery of such a child yields the ethically questionable result that the test has been realized without the informed consent of the person concerned. Therefore, this prenatal testing will be done only exceptionally.

4. *Confidentiality* of individual genetic data is of high concern to the public. Secrecy of these data is, of course, an ethical obligation of the physician in order to preserve the patient's trust as the basis of obtaining all relevant data for diagnosis and treatment. But there are also strong demands, particularly from epidemiological researchers for access to such data in order to gain new knowledge for prevention, diagnosis, or treatment of diseases, i.e. for a common good. The prerequisite of informed consent for such access often cannot be realized, or is liable to a strong selection bias. The future will show whether procedures of protecting anonymity can be found which are safe enough to exclude an erosion of confidentiality. Only if the public is convinced of the confidentiality of individual data will the readiness increase for giving informed consent. An alternative is the legal decision of a community that such data can be used without informed consent – taking corresponding safeguards for granted.
5. An example is the *Icelandic National Database Law* from 1998. This shows the significance of conceptually framing the context of an intervention. To make it concise, I quote from the just published book *Twentieth Century Ethics of Human Subjects Research*:

> The project involves collecting data from the complete Icelandic population in order to analyze the genetic components of a number of diseases. It thus aims at the production of new knowledge, which could lead to new methods of intervention, and which might appropriately be categorized as research involving human subjects. Were one to treat this as an experiment that fell under the guidelines set by the Declaration of Helsinki, all the individuals involved, i.e. the "experimental subjects" would have to give their informed consent to the experiment, and would have to have the opportunity to withdraw at any time from the project. However, in the debates preceding the legislation necessary to establish the database, the protagonists of the project brought forward an alternative interpretation. They suggested that it could be conceptualised in terms of establishing a database for purposes of health policy and management. Viewed from this perspective, the ethical issues raised by the project were those of privacy and data security, and questions about the informed consent of the participants and their right to withdraw became secondary. The negotiations over the wording of the legislation may thus be seen as a story of negotiating interpretations, and redefining terminologies. This illustrates the significance of conceptual categories for the history of research ethics, but also for framing of present day ethical debates. (Roelcke 2004)

Such conceptual framing is guided by a hierarchy of values, such as individual versus common good, or physician as therapist versus physician as researcher.

Modification of brain functioning

Systematic therapeutic modification of pathological brain functioning was started almost 90 years ago with malaria-induced fever, followed by the so-called shock therapies in the 1930s, and psychosurgery in the 1940s. The effectiveness of some of these treatments, particularly of malaria therapy against progressive palsy and ECT against depression, convinced most psychiatrists, and led to their spread all over the world within a few years. Nevertheless, the Nobel Prize Committee hesitated for several years to award the prize to the inventor of the malaria treatment, the Viennese psychiatrist Wagner von Jauregg, the only psychiatrist to win the Nobel Prize, because the psychiatrist member of the committee considered him to be a criminal, since four of the first ten patients died during the course of the malaria therapy (*Wagner v. Jauregg 1950*). Ottosson and Fink have just published a convincing book on ethical dilemmas with ECT. The main conclusion is that ECT today is the most effective and safe treatment against special conditions but the principle of justice, i.e. the equal access to it, is widely violated (Ottosson et al. 2004).

Nowadays all of these treatments, except ECT, are obsolete, mainly because of severe side effects. This is due to the fact that these treatments are apparently very unspecific and rough interventions into the brain, and that the psychotropic drugs coming into use since the early 1950s have been safer and have

promised to be more specific. Up to now the development of psychotropic drugs based biological psychiatry on a steadily growing, tremendous new knowledge of brain chemistry and brain function. The implied ethical issues are manifold and have been more or less recognized since the beginning of this development, but will demand solutions again and again with the introduction of new techniques. According to the psychiatric historian Musto 'the physician's desire to provide quick, effective, economical care, overconfidence about the potential of new technologies to treat intractable diseases, and public enthusiasm' have led, and with every promising new intervention may lead again, to *overuse* and misuse. This conflicts with the best interests of patients as well as with the ethical principle of non-maleficence. These ethical issues will also be inherent to the development of new biological treatments based on specific brain interventions.

1. The term *neurotechnology* comprises new techniques to modify specifically more or less defined brain functions by pharmacological substances, or by activating neuronal stem cells for neurogenesis or specific cerebral areas by transcranial magnetic stimulation (TMS), or by implantation of neuronal tissues or computer–brain interfaces. The hope for the near future is to gain more specificity by defining targets for interventions on the molecular level or on the level of neuronal systems (Elger et al. 2004) that will improve the so-called therapeutic breadth, i.e. the relationship between efficacy and side effects.

   Such interventions will be not only primarily biological ones but also psychological or social ones. They will be based on knowledge of environmental interactions with the brain, e.g., changing the expression of genes by specific sensorial stimuli, or by traumatic stress, or by specific types of psychotherapy. Ethical issues with such interventions, particularly those into the developing brain and with long-lasting effects, may concern the values involved, e.g., the image of man, the self-recognition of personal identity, the tension between reductionistic and integrated approaches, the question of misuse, among possible others. In any case, such developments must be scrutinized with regard to possible new ethical issues.

   In order to avoid an uninformed and emotionalized public discussion, scientists, including psychiatrists, should initiate a public debate aiming at informing the public of the knowledge we have about interventions, and of their benefits, risks, and limits. When we do this, we should clearly separate the empirical facts from their moral evaluation. Furthermore, there is another line to be observed: the border between treatment of diseases of the ill and enhancement of the abilities of healthy people, i.e. between the so-called health system and the rapidly growing life style and wellness market.
2. Nevertheless, due to this unregulated grey zone, industry tries to participate increasingly in the huge financial cake of the so-called health system by convincing physicians and the public as well of the new promising chances to *prevent diseases* by biological means, e.g., by functional foods (e.g., nutrigenomics), and particularly by measures of both *compensating* minor somatic or psychic disadvantages (e.g., blemishes or shyness) and *enhancing* human capabilities and strengths (e.g., cognitive efficiency or creativity). This evolving instrumentalisation of one's own body is a fundamental ethical issue questioning the underlying image of man as well as its compensation from solidarity systems. There are difficulties in establishing clearly the line between therapeutic and enhancing procedures in cosmetic surgery, or sports medicine, or interventions against infertility or minor difficulties in memory or impulse control or problem solving. And there are many uncertainties about empirical facts: What are the effects of a badly wanted substance against memory disturbances, e.g. MEM 1414 (a molecule which 'increases CREB (the cAMP response element-binding protein) that, in turn, activates genes to produce proteins that strengthen the synapse' (E Kandel in Farah et al. 2004) in healthy people? Will continuously present bad memories diminish their coping capacity, or strengthen a desire to block them by another substance? What is the (long-term) safety of such drugs as methylphenidate or modafinil in healthy people, e.g., the question of dependency or of a premature cognitive decline in old age? Should the safety of such *cognitive doping* be proven and access be controlled? Are the ethical implications of cognitive enhancement at least as serious as those of somatic doping in sports?

Self manipulation of human beings has been known for thousands of years, e.g., by psychotropic substances such as vegetable alkaloids, nicotine or alcohol, or by psychological methods such as meditation. However, it seems to be a new stage in the development of mankind that the human being is now capable of deliberately and specifically manipulating his own brain function with perhaps

long-lasting effects. The issue of *enhancement* entered into the discussion when it was found that methylphenidate not only was successful in young people with attention deficit–hyperactivity disorder (ADHD), but also enhanced cognitive abilities such as problem solving in healthy people. Thus, up to one-third of students in some schools in the United States use it, and healthy students in colleges do so as well. In the meantime it is an issue of increasing concern. The New York Academy of Sciences held a meeting on this topic in June 2003 and published the results in May 2004 (Farah et al. 2004).

Will the availability of cognitive enhancement exert an incentive for its use in order to enable one's self to compete successfully with other students or colleagues? Will such cognitive doping decrease the diversity of populations (Butcher 2003)? Will it intensify or diminish social inequality, either because only wealthy people can afford it or because its distribution to all may be cheaper than higher education for all? Would it be ethical to burden financing systems that are based on solidarity against diseases with costs for cognitive doping for healthy people? How will cognitive enhancement affect 'our understanding of what it means to be a person, ... to do meaningful work, and to value life in all its imperfection' (Farah et al. 2004). Therefore, the ethical implications of enhancing mental or psychic strengths will become a major ethical issue in the future of psychiatry.

Analogously, anti-aging will also become a major topic with relevance for psychiatry. In a recent discussion of pro and con arguments about anti-aging, the former arguments were judged more important than the latter (Mackay 2003). Some biogerontologists foresee a postaging world in which aging will be 'under the same degree of control that we currently have over most infectious diseases'. They declare the refusal of such ideas as irrational (de Grey 2004). However, such 'irrational' ideas concern the human condition (conditio humana), e.g., repercussions of the concept of the finiteness of life on the individual life course. Reflections on the human condition are deeply rooted and will change only very slowly if a fundamental change in the human condition may perhaps develop in the very distant future.

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Angell M. 2000. Is academic medicine for sale? (Editorial). New Eng J Med 342(20):1516–1518.

Appelbaum PS, Grisso T. 1995. The MacArthur treatment competence study. I Mental illness and competence to consent to treatment. Law Hum Behav 19(2):105–126.

Bekelman JE, Li Y, Gross CP. 2003. Scope and impact of financial conflicts of interest in biomedical research: A systematic review. J Am Med Assoc 289:454–465.

Butcher J. 2003. Cognitive enhancement raises ethical concerns: Academics urge pre-emptive debate on neurotechnologies. The Lancet 362:132–133.

Chalmers I. 1990. Underreporting research is scientific misconduct. J Am Med Assoc 263(10):1405–1408.

Chalmers I. 2002. Lessons for research ethics committees. Lancet 359:174–174.

Cho MK, Shohara R, Schissel A, Rennie D. 2000. Policies on faculty conflicts of interest at US universities. J Am Med Asoc 284(17):2203–2208.

DeAngelis CD. 2000. Conflict of interest and the public trust. J Am Med Asoc 284(17):2237.

DeAngelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB. 2004. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. J Am Med Asoc 292(11):1363–1364.

de Grey AD. 2004. Biogerontologists' duty to discuss timescales publicly. Ann NY Acad Sci 1019:542–545.

Drazen JM, Curfman GD. 2002. Financial associations of authors. New Engl J Med 346(24):1901–1902.

Elger CE, Friederici AD, Koch C, Luhmann H, Malsburg C von der, Menzel R, Monyer H, Rösler F, Roth G, Scheich S, Singer W. 2004. Das Manifest. Elf führende Neurowissenschaftler über Gegenwart und Zukunft der Hirnforschung. Gehirn Geist 30–37.

Feuerstein G, Kollek R, Schmedders M, van Aken J. 2003. Irreführende Leitbilder. Zum Mythos der Individualisierung durch pharmakogenetische Behandlungskonzepte. Eine kritische Anmerkung. Ethik Med 15(2):77–86.

Farah MJ, Illes J, Cook-Deegan R, Gardner H, Kandel E, King P, Parens E, Sahakian B, Wolpe PR. 2004. Neurocognitive enhancement: What can we do and what should we do? Nat Rev Neurosci 5:421–425.

Helmchen H. 2000. Research involving incompetent patients. A current problem in light of German history. In: Okasha A, Arboleda-Flórez J, Sartorius N, editors. Ethics, culture and psychiatry. Washington, DC: American Psychiatric Association. pp 147–166.

Helmchen H. 2002. Biomedizinische Forschung mit einwilligungsunfähigen Erwachsenen. In: Taupitz J, editor. Das Menschenrechtsübereinkommen zur Biomedizin des Europarates – taugliches Vorbild für eine weltweit geltende Regelung?. Berlin, Heidelberg, New York: Springer. pp 83–115.

Korn D. 2000. Conflicts of interest in biomedical research. J Am Med Asoc 284(17):2234–2237.

Korn D. 2002. Scientific misconduct: the state's role has limits. Nature 420(6917):739.

Mackay T. 2003. An ethical assessment of anti-aging medicine. J Anti Aging Med 6(3):187–204.

Macklin R. 2001. Bioethics and public policy in the next millennium: Presidential address. Bioethics 15(5–6):373–381.

Müller DJ, Shinkai T, De Luca V, Kennedy JL. 2004. Clinical implications of pharmacogenomics for tardive dyskinesia. Pharmacogenomics J 4:77–87.

Nuffield Council on Bioethics. 2002. The ethics of research related to healthcare in developing countries. London: Nuffield Council on Bioethics.

Ottosson JO, Fink M. 2004. Ethics in electroconvulsive therapy. New York, Hove: Brunner-Routledge.

Roelcke V. 2004. Introduction. In: Roelcke V, Maio G, editors. Twentieth Century ethics of human subjects research. Stuttgart: Franz Steiner Verlag. pp 13–14.

Shalala D. 2000. Protecting research subjects – What must be done. New Engl J Med 343(11):808–810.

Vollmann J, Bauer A, Danker-Hopfe A, Helmchen H. 2003. Competence of mentally ill patients: A comparative empirical study. Psychol Med 33:1463–1471.

Vollmann J, Kühl KP, Tilmann A, Hartung HD, Helmchen H. 2004. Einwilligungsfähigkeit und neuropsychologische Einschränkungen bei dementen Patienten. Nervenarzt 75:29–35.

Wagner v. Jauregg J. 1950. Lebenserinnerungen. Wien: Springer.

Ward HJT, Cousens SN, Smith-Bathgate B, Leitch M, Everington D, Will RG, Smith PG. 2004. Obstacles to conducting epidemiological research in the UK general population. Br Med J 329:277–279.

WFSBP. 2004. Proposal of recommendations. Ethical implications of relationships between psychiatrists and pharmaceutical industry. E-version: www.wfsbp.org/ethics

The World Journal of Biological Psychiatry

Publisher
Taylor & Francis
Box 12 Posthuset
Biskop Gunnerusgt. 14A
NO-0051 Oslo, Norway
Tel: + 47 23 10 34 60
Fax: + 47 23 10 34 61
E-mail: post@tandf.no

Printers
Typeset by Datapage International Ltd., Dublin, Ireland
Printed by Hobbs the Printers, Hampshire, UK

The World Journal of Biological Psychiatry is one of the numerous benefits available to *World Federation of Societies of Biological Psychiatry* registered members, to whom The journal is sent free of charge and accessible on-line in the members only section of the Federation's web site www.wfsbp.org. Please contact the WFSBP Global Headquarters at global.headquarters@wfsbp.org for more information.

Subscription Information
The World Journal of Biological Psychiatry, ISSN print edition 1562-2975, online edition 1814-1412, is published four times a year. Visit our webpage for more information: www.tandf.no/wjbp

Annual subscription rates for volume 6, 2005: Institutions: $320, individuals $140. Postage included. Air speed delivery to subscribers worldwide. Supplements are supplied free of charge to all subscribers. Free electronic access is available to all subscribers of the print version.

Orders for subscription, back issues and change of address should be sent to: Taylor & Francis, Customer Services, T&F Informa UK Ltd, Sheepen Place, Colchester, Essex, CO3 3LP, United Kingdom. Tel: + 44 (0) 20 7017 5544. Fax: + 44 (0) 20 7017 5198. E-mail: tf.enquiries@tfinforma.com

Taylor & Francis retains a three year back issue stock of journals. Older volumes are held by our official stockists: Periodicals Service Company (http://www.periodicals.com/tandf.html) 11 Main Street, Germantown, NY 12526, USA, to whom all orders and enquiries should be addressed. Tel: + 1 518 537 4700. Fax: + 1 518 537 5899. E-mail: psc@periodicals.com

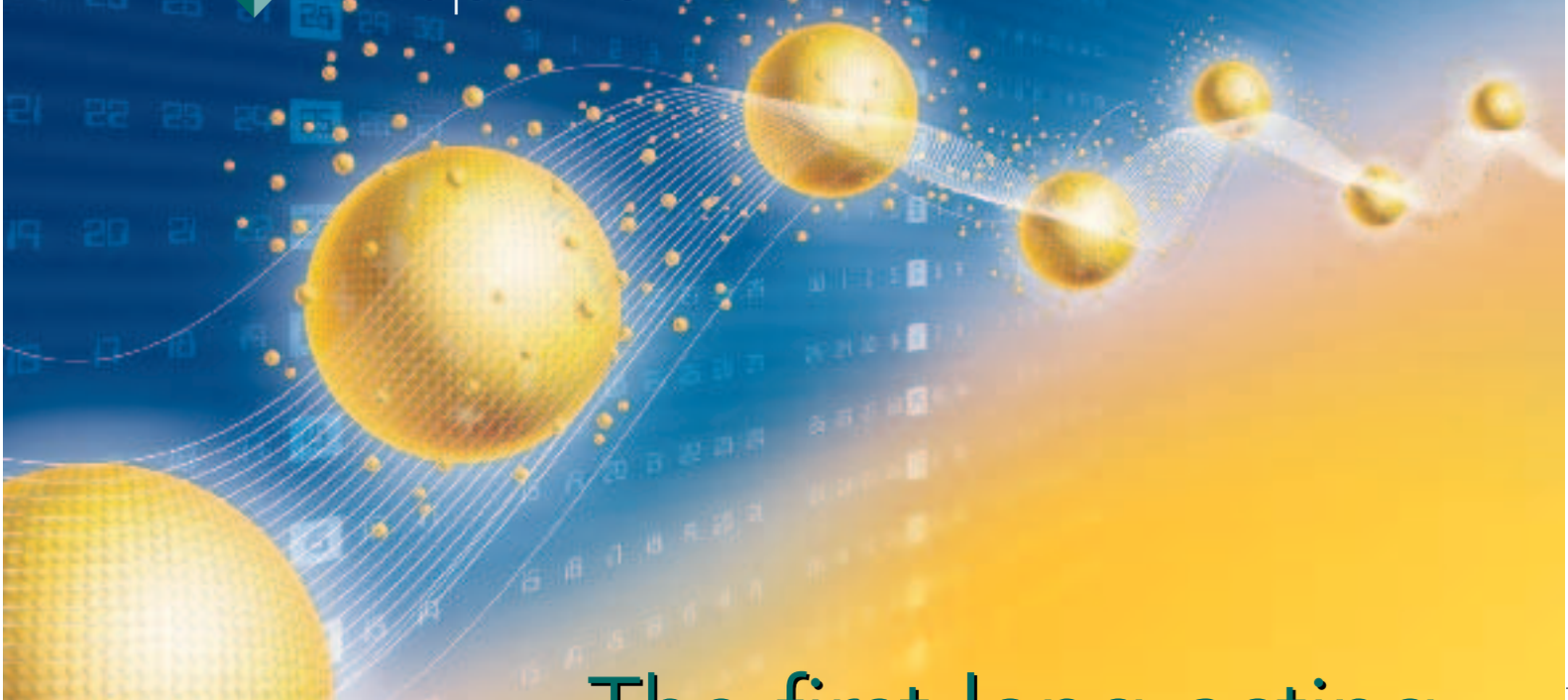
Correspondence concerning publishing matters, copyright, permissions and reprints should be addressed to: Taylor & Francis, PO Box 12 Posthuset, NO-0051 Oslo, Norway. Tel: + 47 23 10 34 60. Fax: + 47 23 10 34 61. E-mail: post@tandf.no
The World Journal of Biological Psychiatry (USPS permit pending) is published in March, May, August and November. The 2005 institutional subscription price is $320. Periodicals postage pending at Champlain, NY, by US Mail Agent IMS of New York, 100 Walnut Street, Champlain, NY.
US Postmaster: Please send address changes to sWBP, PO Box 1518 Champlain, NY 12919, USA.

Indexed in:
Index Medicus/MEDLINE, Science Citation Index Expanded, ISI Alerting Services, Current Contents/Clinical Medicine, Current Contents/Life Sciences, NeuroScience Citation Index

NEW IN PSYCHOSIS

Risperdal® CONSTA™

risperidone LONG-ACTING INJECTION



The first long-acting atypical provides constant coverage for long-term improved stability

ABBREVIATED PRESCRIBING INFORMATION **Risperdal® Consta™ Injection** (Risperidone). See SmPC before prescribing. **USES:** Schizophrenia. Other psychotic conditions, in which positive and/or negative symptoms are prominent. Not licensed for behavioural symptoms of dementia. **DOSAGE(IM):** Adults: 25mg every 2 weeks (alternate buttocks); consider 37.5mg if stabilised on more than 4mg/day oral. Consider 12.5mg increase after 4 weeks. Maximum; 50mg every 2 weeks. Ensure prior tolerability with oral risperidone. Supplement with oral risperidone for first 3 weeks as appropriate. Elderly: 25mg every 2 weeks, plus oral cover as above. Renal and hepatic impairment: Caution. 25mg every 2 weeks if minimum 2mg oral tolerated following titration. Children and adolescents under 18 years: Not studied. **CONTRA-INDICATIONS:** Hypersensitivity. **PRECAUTIONS:** Not recommended for behavioural symptoms of dementia because of threefold risk of cerebrovascular adverse events. If history of CVA/TIA, consider risk carefully. Care with other risk factors for cerebrovascular disease. Orthostatic hypotension. Cardiovascular disease. Drugs prolonging QT. Reduce dose if hypotension. If tardive dyskinesia consider stopping all antipsychotic drugs. Parkinson's disease. Epilepsy. If Neuroleptic Malignant Syndrome, stop all antipsychotics. Advise of potential for weight gain. Advise not to drive or operate machinery if alertness affected. Acute withdrawal symptoms, recurrence of psychoses. Recommend gradual withdrawal. **PREGNANCY:** If benefits outweigh risks. **LACTATION:** Avoid. **INTERACTIONS:** Centrally acting drugs, dopamine agonists, hepatic enzyme-inducing drugs. **SIDE EFFECTS:** Insomnia, agitation, anxiety, headache, somnolence, dizziness, impaired concentration, blurred vision, sexual dysfunctions, urinary incontinence, rash, other allergic reactions. Extrapyramidal symptoms, orthostatic dizziness, hypotension, tachycardia and hypertension. Increased plasma prolactin, hepatic enzymes, changes in white cell and platelet levels. Oedema, water intoxication with hyponatraemia, tardive dyskinesia, body temperature dysregulation and seizures. CVAs. Very rarely: hyperglycaemia and exacerbation of pre-existing diabetes. Weight gain or loss, depression, fatigue, nervousness, sleep disorder, apathy, syncope, injection site reaction. **ACTIVE INGREDIENT:** Risperidone **PRESENTATIONS, PACK SIZES:** 25mg prolonged-release injection; 37.5mg prolonged-release injection; 50mg prolonged-release injection. Full prescribing information available upon request.

JANSSEN-CILAG Organon