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# The World Journal of Biological Psychiatry

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### Instructions to Authors

## Editorial

### Broadening the Treatment Indication: Is the Term Antipsychotic still Justified?

Most researchers and clinicians would agree that the terminology chosen for a group of medication should be logical and characteristic for the disease treated. However, for the group of atypical antipsychotics that show a predictable broadening of treatment indications in addition to the treatment of schizophrenia, this is not the case.

Neuroleptics - also called typical, conventional or classical neuroleptics - were originally developed for the indication of schizophrenia. The term neuroleptic indicates that they are working on the "neuron". No further specification was associated with this name. However, it soon emerged that some compounds of this class were not only indicated in schizophrenia, but also for states of excitement like mania or organic psychosis. Interestingly, clinicians also started using low or medium potency neuroleptics for the augmentation of treatment-resistant depression and further psychopathological states within the area of "psychosomatic symptomatology", which very likely, if diagnosed correctly, would be found in the field of anxiety disorders. For the latter indication, for instance, the depot formulation of flurspirilene ("IMAP") has been widely used in Germany, mostly by general practitioners but also by doctors without a specialisation in psychiatry. The usage of typical neuroleptics was always questioned, since there is a threat to develop tardive dyskinesia and also depressive symptomatology. For the diagnosis of schizophrenia, the term pharmacogenic depression has been established when patients receive typical neuroleptics.

Although clozapine, with its specific pharmacodynamic properties, has been around for about 40 years in European research and treatment facilities, it was not until the introduction of olanzapine, risperidon, quetiapine, ziprasidone and zotepine that the group of "atypical antipsychotics" was defined. The term atypical antipsychotics was probably established in order to show - from a clinical point of view - a clear distinction from the group of typical neuroleptics that was associated with the occurrence of extrapyramidal motor side effects (EPS), the lack of efficacy for treatment or even the worsening of negative, affective and cognitive symptoms. Moreover, the term atypical antipsychotics described - from a pharmacodynamic point of view - the combined anti-serotonergic (5-HT<sub>2</sub>) and anti-dopaminergic mechanism of action - with the exception of amisulpride and aripiprazole that have other specific pharmacodynamic properties modulating the dopaminergic system, but clinically also offering the aforementioned properties.

The introduction of the terminology antipsychotic was insofar problematic since, as described above, the older group of neuroleptics was already used in indications other than schizophrenia. As could have probably been predicted from a pharmacodynamic perspective, for instance the 5-HT<sub>2</sub> blocking properties of the newer compounds, the group of atypical antipsychotics has now a growing potential for use in indications other than schizophrenia: indications like bipolar disorder, treatment-resistant depression, posttraumatic stress disorder, generalised anxiety disorder and obsessive-compulsive disorder. The term antipsychotic is therefore misleading and patients taking this group of medication are not likely to comply if they read, for instance, in the package insert or in the available literature that can nowadays easily be obtained from the internet, that this medication is used for the group of psychosis, a diagnosis that all patients with anxiety disorders substantially fear as being part of their illness.

It is always hard to predict how the terminology will develop further but, for the sake of clarity, the old term neuroleptic, meaning to treat the neuron, might be more realistic, practical and - from a patient's point of view - non-discriminating. However, as the atypical antipsychotics are clearly not only antipsychotic, further nomenclature reflecting their efficacy in non-psychotic states as well as psychosis will be desired. In this sense, a nomenclature that refers to their mode of action rather than to the disease for which the medication was first developed, might be useful. A terminology based on generations (like 1st, 2nd, 3rd or 4th etc. generation neuroleptics) or even a broader term, like psychotropic, might also soon be outdated and not applicable in daily communication of researchers as well as in treatment settings.

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## CSF Markers for Alzheimer's Disease: Total Tau, Phospho-tau and A $\beta$ 42

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### Summary

Today we have the first therapeutic compounds for treatment of Alzheimer's disease (AD) e.g. acetylcholine esterase inhibitors and in the near future we may expect new compounds such as  $\gamma$ - and  $\beta$ -secretase inhibitors. This has demanded increased accuracy in the diagnosis of AD and thus, among other possible approaches, diagnostic markers in the cerebrospinal fluid (CSF) have become a rapidly growing research field. Especially early in the course of the disease, when correct diagnosis is most difficult, such biomarkers would be especially valuable as one might expect the compounds to have the greatest potential of being effective. Two of the defining lesions in AD brains are senile plaques and neurofibrillary tangles with  $\beta$ -amyloid (A $\beta$ ) and tau proteins as the main components respectively. A $\beta$  and tau proteins are secreted to body fluids including plasma and cerebrospinal fluid (CSF). In this paper we review CSF markers for AD, with focus on their role in the clinical diagnosis. Reduced CSF levels of the 42 amino acid form of A $\beta$  (A $\beta$ 42) and increased CSF levels of total tau (T-tau) in AD have been found in numerous studies, with high sensitivity figures. However, the specificity against other dementias is lower. The addition of phospho tau (P-tau) seems to increase the specificity, since normal levels are found in other dementias and in cerebrovascular disease. An increasing number of studies suggests that these CSF markers perform well enough to have a role in the clinical work-up of patients with dementia if used together. We stress that the CSF markers should be combined with the clinical information and brain-imaging techniques.

**Key words:** Alzheimer's disease, mild cognitive impairment (MCI), tau, phosphorylated tau,  $\beta$ -amyloid (A $\beta$ ), biochemical markers, cerebrospinal fluid (CSF).

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### Introduction

The total cost of the care of patients with dementia for society is substantial, and for Sweden the direct cost is estimated to be around 0.4 billion Euro per million inhabitants (Wimo and Jönsson 2000). Moreover, with a rapid increase in elderly population, this cost is bound to increase further if nothing is done. Alzheimer's disease (AD) is the most common form of dementia and has already become one of the most costly affections for modern society, with a substantial impact on the family caregiver and the entire health system. The vast majority of AD has no clear family history and is classified as sporadic AD (Blennow and Skoog 1999).

The diagnosis is currently based on clinical and neuropsychological evaluation and the absence of other known causes of dementia as outlined by the NINCDS-ADRDA (McKhann et al. 1984), and diagnosis is only definite after death at autopsy. Studies have shown that the accuracy of the diagnosis runs from 65% to at most 90% with figures emanating from academic centres with special interest in AD, and are based on patients in the later stages of the disease who were followed for several years before the confirming autopsy (Tierney et al. 1988; Galasko et al. 1994; Geddes et al. 1997). The accuracy at primary care level and in general hospitals might be even lower, and this may especially be the case in the early phase of the disease where symptoms are vague and indistinct.

In view of existing (Giacobini 2000) and emerging therapeutic compounds there is a great need for reliable biochemical diagnostic markers in the diagnosis of dementia, especially for AD. This is not least important early in the course of the disease, before neurodegeneration is too severe and widespread, and where the diagnostic problems are known to be most difficult.

The cerebrospinal fluid (CSF) is in direct contact with the extracellular space of the brain, thus biochemical changes in the brain may be reflected in the CSF, and since AD pathology is restricted to the brain, CSF is an obvious source of biomarkers for AD. It has been suggested that a diagnostic marker for AD should reflect the central pathogenic process of the disease, i.e. the degeneration of the neurons and their synapses (Consensus report 1998). Two of the defining lesions in AD are senile plaques (SP) and neurofibrillary tangles (NFT). Biomarkers for these pathogenic processes are, respectively, Ab42, normal (total) tau protein (T-tau), and phosphorylated tau protein (P-tau) (Figure 1).

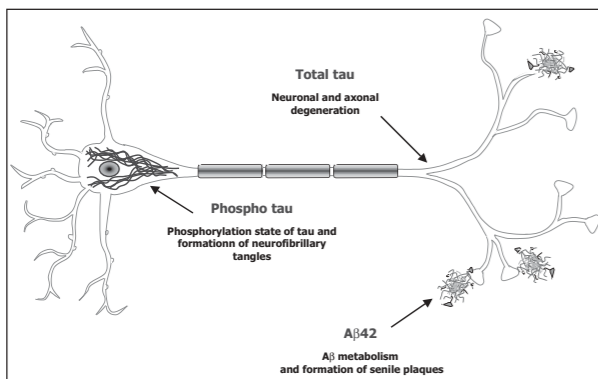


Figure 1 Schematic drawing of a neuron with three senile plaques near the synapses and neurofibrillary tangles in the cytoplasm. The three cerebrospinal fluid markers for Alzheimer disease, and the pathogenic process they possibly reflect, are shown.

• **Total tau (T-tau)**

Tau is a normal brain phosphoprotein, which binds to microtubules in the neuronal axon, thereby promoting assembly and stability (Goedert 1993). There are six different isoforms of tau in the human brain (Figure 2). Three different ELISAs have been developed for measurement of T-tau in CSF (Vandermeeren et al. 1993; Blennow et al. 1995; Vigo-Pelfrey et al. 1995). Using these ELISAs, a moderate to marked increase in CSF T-tau in AD has consistently been demonstrated in more than 50 studies.

The most commonly used ELISA, INNOTEST™ hTAU Ag, for measurement of T-tau in CSF (Blennow et al. 1995) uses monoclonal antibodies that detect all isoforms of tau independent of phosphorylation state (Figure 2). There are 39 studies, including about 2400 AD cases and 1250 controls, in which sensitivity and specificity figures have been given, or can be calculated from graphs (Table 1). These studies show that the mean sensitivity to discriminate between AD and normal aging is approximately 82%, while the specificity is approximately 88%, and the mean level of increase in AD compared with controls is above 300% (Table 1).

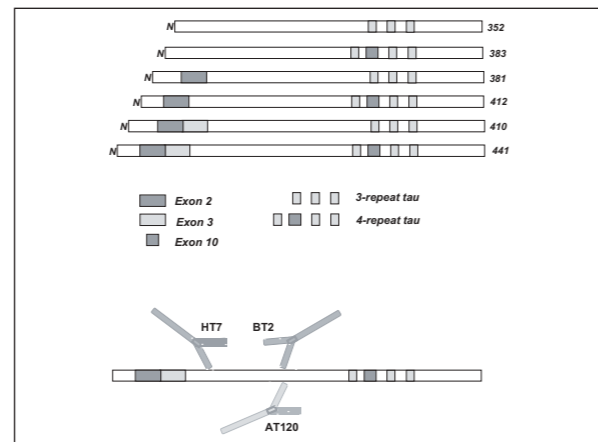


Figure 2 A) Schematic picture of human tau protein with the six isoforms. Alternatively spliced exons (exon 2, 3 and 10) are shown. At top the smallest tau isoform (352 amino acids) containing three repeat domains. At bottom the largest tau isoform (441 amino acids) containing four repeat domains (exon 10 spliced in) and two extra domains from exons 2 and 3. B) Principles for an ELISA (Blennow et al. 1995) specific for total tau (T-tau), in which three monoclonal antibodies (AT120, HT7 and BT2) are used. All antibodies recognize tau irrespective of phosphorylation state, and are specific for epitopes outside the alternatively spliced exons.

There is an age-associated increase in CSF T-tau in non-demented individuals (Sjögren et al. 2001c; Buerger et al. 2003). Thus, age-adjusted reference values should be considered when T-tau is used diagnostically, which improves the separation between AD and other brain disorders (Buerger et al. 2003).

However, high T-tau in CSF is also found in a proportion of cases with other dementia disorders, such as frontotemporal dementia (Green et al. 1999; Molina et al. 1999) and Lewy body dementia (Andreasen et al. 2001). In contrast, in patients with other types of dementia (e.g. alcoholic dementia), chronic neurological disorders (e.g. Parkinson's disease) and psychiatric disorders (e.g. depression), elevated CSF T-tau levels are found only in occasional cases (Blennow et al. 1995; Molina et al. 1999; Morikawa et al. 1999; Urakami et al. 1999).

Tau protein is normally secreted to the CSF. The level of T-tau in CSF probably reflects the degree of neuronal degeneration and damage (Blennow et al. 1995). Thus, a transient increase in T-tau is found after acute stroke, with a positive correlation between T-tau and infarct size measured by CT (Hesse et al. 2000). A very marked increase is also found in Creutzfeldt-Jakob disease, with very rapid degeneration (Otto et al. 1997).

• **β-amyloid (Aβ42)**

Aβ is a cleavage product from the amyloid precursor protein (APP) (Figure 3). In the first step in the production of Aβ, APP is cleaved after position 671 by β-secretase, resulting in the release of a large N-terminal fragment called β-secretase cleaved soluble APP (b-sAPP), and in

Table 1 Performance of CSF total tau (T-tau) in the diagnosis of Alzheimer's disease

Country	Study	AD number	AD sensitivity	Percent increase	Control number	Cont specificity	Comment
EU	Blennow 1995	44	84	283	31	97	
Japan	Arai 1995	70	100	858	19	100	
EU	Jensen 1995	15	95	661	22	100	Values as tau/total protein. 8 FAD, 7 sporadic AD.
EU	Riemenschneider 1996	11	95	446	19	95	
EU	Rösler 1996	16	88	n.g.	10	100	
EU	Andreasen 1998	43	95	419	18	94	Community-based patient sample Mixed AD/vascular dementia
	" - "	11	100	398			
Japan	Arai 1998	69	89	443	17	100	
Japan	Kanai 1998	93	40	226	41	98	
EU	Kurz 1998	40	89	442	36	97	
EU	Mecocci 1998	29	52	205	15	73	
Japan	Nishimura 1998	163	66	227	65	83	
Japan	Shoji 1998	55	31	214	34	97	
EU	Tapiola 1998	81	58	179	33	88	Neurological controls
EU	Vanderstichele 1998	81	90	178	15	67	
Japan	Morihara 1998	11	91	312	14	100	
EU	Andreasen 1999a	407	93	304	93	86	Controls including depression
EU	Burger nee Buch 1999	15	87	212	25	76	< 70 years
	" - "	23	83	n.a.	22	46	>70 years
EU	Green 1999	17	76	405	9	100	
EU	Hampel 1999	25	80	231	19	85	
EU+USA	Hulstaert 1999	150	79	218	100	70	"Non-AD" controls
Japan	Ishiguro 1999	36	97	n.g.	20	50	
EU	Martinez 1999	10	100	544	10	90	
Japan	Morikawa 1999	36	92	505	23	95	
USA	Kahle 2000	30	63	247	16	75	
	" - "	5	80	n.g.			Neuropathological AD
Japan	Kanemaru 2000	24	83	400	19	95	
EU	Sjögren 2000a	60	79	242	32	82	
EU	Sjögren 2000b	21	76	200	18	85	Early onset AD
	" - "	21	57	186			Late onset AD
EU	Gottfries 2001	43	95	204	n.a.	n.a.	Compared with reference values.
Japan	Itoh 2001	236	85	303	95		Approximate sensitivity and specificity
EU	Kapaki 2001	38	90	358	47	92	
Japan	Maruyama 2001	54	87	351	15	93	
EU	Rösler 2001	27	89	320	49	100	
EU	Sjögren 2001b	47	77	237	12		
EU	Buerger 2002a	80	81,3	n.g.	21	91	
Japan	Hu 2002	52	79	226	56	100	
EU	Briani 2002	9	67	293	17	88	
EU	Mulder 2002	20	90	223	20	90	
EU	Sjögren 2002	19	84	269	17	94	
EU	Riemenschneider 2002	74	95	355	40	98	Controls with lumbago
	Sum/mean	2411	81,6	324,3	1184	88,4	

a second step APP is cleaved by the γ-secretase complex releasing free Aβ (Figure 3), which is secreted to the CSF.

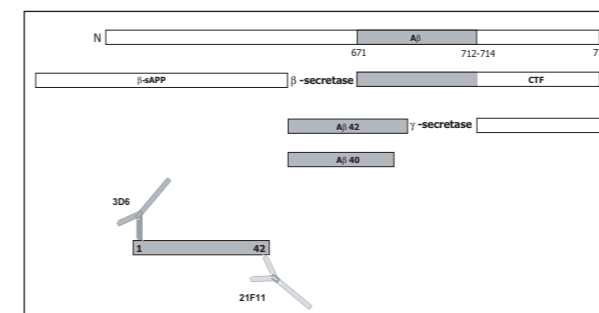


Figure 3 A) Schematic picture of amyloid precursor protein (APP) and the generation of free β-amyloid (Aβ). Aβ is generated through cleavage by two proteases. APP is subsequently cleaved by β-secretase and γ-secretase, releasing free Aβ which is secreted to the CSF. B) Principles for an ELISA (Vanderstichele et al. 1998) specific for Aβ42, in which capture antibody (21F12) is specific for the C-terminus of Aβ (Aβ42) and the detection antibody (3D6) specifically recognizes the N-terminus of Aβ (Aβ1).

There are five different ELISA methods specific to Aβ42 (Mottet et al. 1995; Tamaoka et al. 1997;

Vanderstichele et al. 1998; Jensen et al. 2000; Mehta et al. 2000). Using one of these ELISA methods, an increase in CSF-Aβ42 was found both in patients with AD and in patients with depression (Jensen et al. 1999). Using the other ELISA method, a decrease in CSF Aβ42 to about 50% of control levels has been found in more than 35 studies, while normal CSF Aβ42 has been found in depression (Andreasen et al. 1999b; Sjögren et al. 2000a). These differences may be due to methodological differences (e.g., antibody specificity for Ab isoforms) or differences in patient and control materials.

The principle for the most commonly used ELISA, INNOTEST™ β-AMYLOID(1-42), for measurement of Ab42 in CSF (Vanderstichele et al. 1998) is shown in Figure 3. There are 13 studies, including about 600 AD cases and 450 controls, in which sensitivity and specificity figures have been given, or can be calculated from graphs (Table 2). These studies show that the mean sensitivity to discriminate between AD and normal aging is approximately 86%, while the specificity is approximately 91% (Table 2).

Table 2  
Performance of CSF A $\beta$ 42 in the diagnosis of Alzheimer's disease

Country	Study	AD number	AD sensitivity	Percent decrease	Control number	Cont specificity	Comment
EU	Vanderstichele 1998	81	81	75	51	80	
EU	Andreasen 1999b	53	92	42	21	95	Community-based sample
EU	Andreasen 1999c	16	88	72	15	80	
EU+USA	Hulstaert 1999	150	78	57	100	81	
Japan	Kanemaru 2000	24	96	40	19	95	
EU	Otto 2000	14	93	40	20	95	
EU	Sjögren 2000a	60	93	49	32	n.g.	
EU	Kapaki 2001	38	76	51	47	85	
EU	Rösler 2001	27	78	48	49	100	
EU	Briani 2002	9	55	73	17	94	
EU	Mulder 2002	20	100	46	20	95	
EU	Sjögren 2002	19	100	42	17	94	
EU	Riemenschneider 2002	74	89	37	40	95	
	Sum/mean	585	86,1	51,7	448	90,8	

Low levels are found in Lewy body dementia (Kanemaru et al. 2000; Andreasen et al. 2001), a disorder also characterized by the presence of senile plaques. However, low levels are also found in a percentage of patients with frontotemporal dementia and vascular dementia (Hulstaert et al. 1999; Sjögren et al. 2000a).

The reduction in CSF-A $\beta$ 42 in AD was initially hypothesized to reflect a deposition of the peptide in SP, with lower levels diffusing to the CSF. However, a marked reduction in CSF-A $\beta$ 42 is found in Creutzfeldt-Jakob disease, also in cases without A $\beta$  positive plaques (Otto et al. 2000; Kapaki et al. 2001), and in amyotrophic lateral sclerosis (Sjögren et al. 2002), both disorders without A $\beta$  positive plaques. These findings question the putative relationship between low CSF-A $\beta$ 42 and formation of SP.

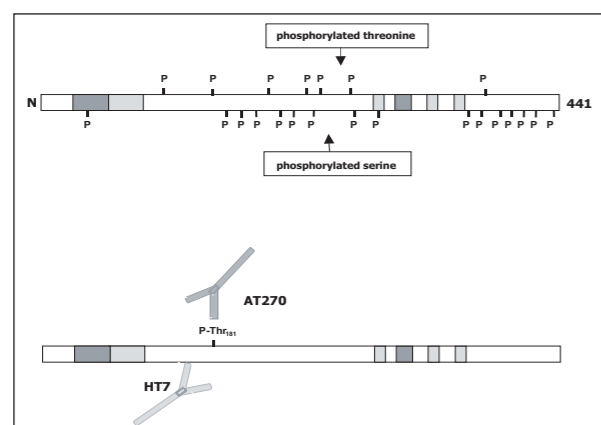


Figure 4  
A) Schematic picture of the largest tau isoform (441 amino acids), with phosphorylation sites, either threonine or serine.  
B) Principles for an ELISA (Vanmechelen et al. 2000) specific for phospho-tau (P-Thr181), in which the capture antibody (HT7) recognizes all forms of tau and the detection antibody (AT270) specifically recognizes tau phosphorylated at threonine 181.

#### • Phosphorylated tau (P-tau)

Numerous phosphorylation sites are found on human tau (Figure 4). When hyperphosphoryl-

ated, as in AD, tau protein loses its ability to act as the "glue" that binds the microtubules together, thereby causing instability in the axon and diminishing its transport ability (Ferreira et al. 1989; Iqbal and Grundke-Iqbal 1997) and promotes aggregation of tau with subsequent formation of NFT (Goedert 1993).

The principles for an ELISA (Vanmechelen et al. 2000) for measurement of tau phosphorylated at threonine 181 (P-Tau<sub>181</sub>), INNOTEST™ PHOSPHO-TAU<sub>(181P)</sub>, are given in Figure 4. Several other ELISAs have been developed for different phosphorylated epitopes of tau, including threonine 181 and 231 (P-tau<sub>181+231</sub>) (Blennow et al. 1995), threonine 231 and serine 235 (P-tau<sub>231+235</sub>) (Ishiguro et al. 1999), serine 199 (P-tau<sub>199</sub>) (Ishiguro et al. 1999), threonine 231 (P-tau<sub>231</sub>) (Kohnken et al. 2000), and serine 396 and 404 (P-tau<sub>396+404</sub>) (Hu et al. 2002).

An increased level of P-tau in CSF in AD has been found using all the different assays (Table 3). The sensitivity for P-tau to discriminate between AD and normal aging is about the same, or slightly lower, as for T-tau, around 75%. However, further studies are needed to determine the true sensitivity level for P-tau. Interestingly, the specificity for P-tau to differentiate AD from other dementias seems to be higher than for T-tau and Ab42. Normal levels of P-tau in CSF are found in VAD and in frontotemporal dementia (Sjögren et al. 2001a), and in Lewy body dementia (Parnetti et al. 2001), suggesting that this analysis may help in the discrimination between AD and these dementias.

After acute stroke, there is a marked increase in CSF total tau, while CSF phospho-tau does not change (Hesse et al. 2001). Further, despite a very marked increase in CSF T-tau in Creutzfeldt-Jakob disease, there are no major changes in CSF P-tau (Riemenschneider et al. 2003). This finding suggests that CSF phospho-tau is not simply a marker for neuronal damage,

Table 3  
Performance of CSF phospho tau (P-tau) in the diagnosis of Alzheimer's disease

Country	Study	P-tau epitope	AD number	AD sensitivity	Percent increase	Control number	Cont specificity	Comment
EU	Blennow 1995	P-Thr181 + P-Thr231	40	88	348	31	97	
EU	Vanmechelen 2000	P-Thr181	41	44	148	17	94	
EU+USA	Parnetti 2001	P-Thr181	80	84	n.g.	40	88	
EU	Sjögren 2001a	P-Thr181	60	37	145	17	94	
EU	Sjögren 2002	P-Thr181	19	58	164	17	94	
Japan	Ishiguro 1999	P-Thr231 + P-Ser235	36	53	n.g.	20	100	"Non-AD" controls
Japan	Ishiguro 1999	P-Ser199	36	94	n.g.	20	80	"Non-AD" controls
Japan	Itoh 2001	P-Ser199	236	85	317	95	84	
USA	Kohnken 2000	P-Thr231	27	85	n.g.	31	97	
EU	Buerger 2002a	P-Thr231	82	100	n.g.	21	91	
USA+China	Hu 2002	P-Ser396+404	52	83	346	56	98	
	Sum/mean		709	73,7	244,7	365	92,4	

as CSF total tau, but suggests that it specifically reflects phosphorylated tau, and thus possibly the formation of NFT.

#### CSF markers in mild cognitive impairment and in AD

High T-tau and low A $\beta$ 42 in CSF in early AD, i.e. in AD patients with high (>23-25) Mini-Mental State Examination scores, but with dementia (Andreasen et al. 1999a,b; Galasko et al. 1997, 1998; Hulstaert et al. 1999; Kurz et al. 1998; Riemenschneider et al. 1996, 2000) have been found in several studies. As for more severely demented AD cases, the sensitivity figures are about 80-90%, suggesting that these CSF markers are positive early in the disease process.

Several studies have also found high T-tau and low A $\beta$ 42 in CSF in patients with mild cognitive impairment (MCI) without dementia, who later developed AD with clinical dementia (Arai et al. 1997; Andreasen et al. 1999c, 2001; Buerger et al. 2002a). High T-tau was also found to discriminate MCI patients who later progressed to AD from those who did not progress with high sensitivity and specificity (Arai et al. 1997). In the same way, high P-tau in CSF is found in a high proportion of MCI cases (Arai et al. 2000; Andreasen et al. 2002; Buerger et al. 2002b). These findings suggest that these CSF markers may be of use in the clinical identification of AD in the very early phases of the disease.

There is an on-going debate whether CSF P-tau may be of value to predict cognitive decline in MCI cases. In a longitudinal study on 17 AD cases, P-tau<sub>231</sub> declined during the course of AD (Hempel et al. 2001). Further, in a longitudinal-study on 77 MCI cases, high CSF P-tau<sub>231</sub> at baseline was associated with subsequent cognitive decline (Buerger et al. 2002b). Further prospective longitudinal studies are needed to determine the potential of CSF P-tau as a prognostic marker in MCI cases.

#### CSF markers for AD in clinical practice

In two studies, the performance of T-tau (Andreasen et al. 1999a) and the combination of T-tau and A $\beta$ 42 (Andreasen et al. 2001) was evaluated on prospective patient samples and ELISA assays were run each week in clinical neurochemical routine. The analytical variation and stability (analyzed during one year) for these CSF analyses were adequate. Also in clinical practice, the ability of CSF tau (Andreasen et al. 1999a) and the combination of CSF tau and CSF A $\beta$ 42 (Andreasen et al. 2001) to differentiate AD from normal aging, depression and Parkinson's disease was high, while the specificity against other dementias was relatively poor.

However, the addition of P-tau increases the specificity, since normal P-tau levels are found in most cases with frontotemporal and Lewy body dementia, and also in cerebrovascular disease. Thus, the combination of several CSF markers (T-tau, Ab42 and P-tau) will increase the specificity for the diagnosis of AD. A summary of the performance of these CSF biomarkers is given in Table 4.

Although the diagnostic performance of CSF biomarkers for AD is evaluated as isolated tests in scientific papers, they should be used as additions to the clinical evaluation and other investigations in routine clinical practice. An analogy is myocardial infarction, where the clinical diagnosis is based on the combined information from the clinical examination (i.e. typical chest pain), electrocardiogram (e.g. ST-elevation), and biomarkers (e.g. creatine kinase and troponine T). Similarly, the clinical diagnosis of AD should be based on cumulative information from the clinical examination (i.e. memory disturbance and instrumental symptoms), brain-imaging techniques (e.g. SPECT and MRT scans), and CSF biochemical markers.

**Table 4**  
Performance of CSF markers for Alzheimer's disease

Disease	T-tau	P-tau	Ab42
Alzheimer's disease	Moderate / marked increase	Moderate / marked increase	Moderate / marked decrease
Normal ageing	Normal	Normal	Normal
Depression	Normal	Normal	Normal
Alcoholic dementia	Normal	Normal	Normal
Frontotemporal dementia	Normal / mild increase	Normal / mild decrease	Normal / mild decrease
Lewy body dementia	Normal / mild increase	Normal	Mild / moderate decrease
Parkinson's disease	Normal	Normal	Normal
Creutzfeldt-Jakob disease	Very marked increase	Normal, but some cases with mild / moderate increase	Moderate / marked decrease
Vascular dementia	Conflicting data (some studies with normal levels – some with increased)	Normal	Normal / mild decrease
Acute stroke	Increased levels related to the size of the infarct	Normal	Normal

The table presents a summary of the diagnostic performance of CSF markers for Alzheimer's disease based on publications up to October 2002.

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# The Evaluation of Suicide Prevention Activities: State of the Art

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### Summary

One million people commit suicide world-wide every year. The need for suicide prevention is obvious, and very different approaches have been investigated to reduce the number of suicides. Some interventions aim at identified high-risk groups (e.g. support for people after suicide attempt), some at the population as a whole (e.g. restricting the access to means for suicide). There is, however, but little evidence for the efficacy of suicide prevention activities. This can mostly be attributed to methodological problems such as the lack of randomised controlled studies and the fact that the sample size is too small to show an effect. Despite these problems, some interventions showed promising results (e.g. long-term lithium treatment). A main problem, however, is that many people at risk do not get in contact with health care institutions. Moreover, no single approach by itself seems to contribute to a substantial decline in the suicide rate. The authors therefore argue that a combination of different strategies in a multi-level approach might prove to be the most effective.

**Key words:** suicide, prevention, evaluation.

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### Introduction

According to estimates by the World Health Organisation (WHO) about one million people world-wide die from suicide every year. When comparing the suicide rates (per 100,000 population) of different countries there are considerable differences (see Figure 1). There is always the question of reliability when suicide rates are discussed, because suicide can be hidden for several reasons. Therefore the exact figures of suicide rates might even be higher (Bertolote 2000).

There is still considerable debate about suicide, its underlying causes and the way psychological and biological factors interact. Hence there are many different interventions in the field of suicide prevention. Some aim at specific high-risk groups (e.g. long-term lithium treatment for patients suffering from recurrent depression), others at the population as a whole (e.g. restriction of access to means to commit suicide). Figure 2 outlines the different measures of high-risk strategies and population-based strategies in the field of suicide prevention. The evidence for their efficacy, however, is doubtful (Gunnell and Frankel 1994) because there is a lack of valid and persuasive studies. This can be attributed to methodological problems in the field of suicidology. In many studies there is no control group and no randomisation (this is often due to ethical reasons which do not allow an experimental randomisation). In general, sample sizes are too small to show significant effects. In addition, in many cases the outcome criteria used for the evaluation of the studies are weak. Changes in attitudes towards suicidality or the existence of suicidal thoughts were the most frequently used measures. It still remains uncertain that this is a strong predictor for future suicidal behaviour.

This review will present an overview about the state of the art in suicide prevention, exemplifying the different approaches and discussing their efficacy. Table 1 lists studies that investigated changes in suicidality after specific interventions.

### High-risk strategies in suicide prevention

Psychological autopsy studies showed that more than 90 per cent of suicides are committed in the context of a psychiatric disorder (e.g. Lonnqvist et al. 1995). Depressive disorders, alcoholism and schizophrenia were found to be the most important diagnosis associated with

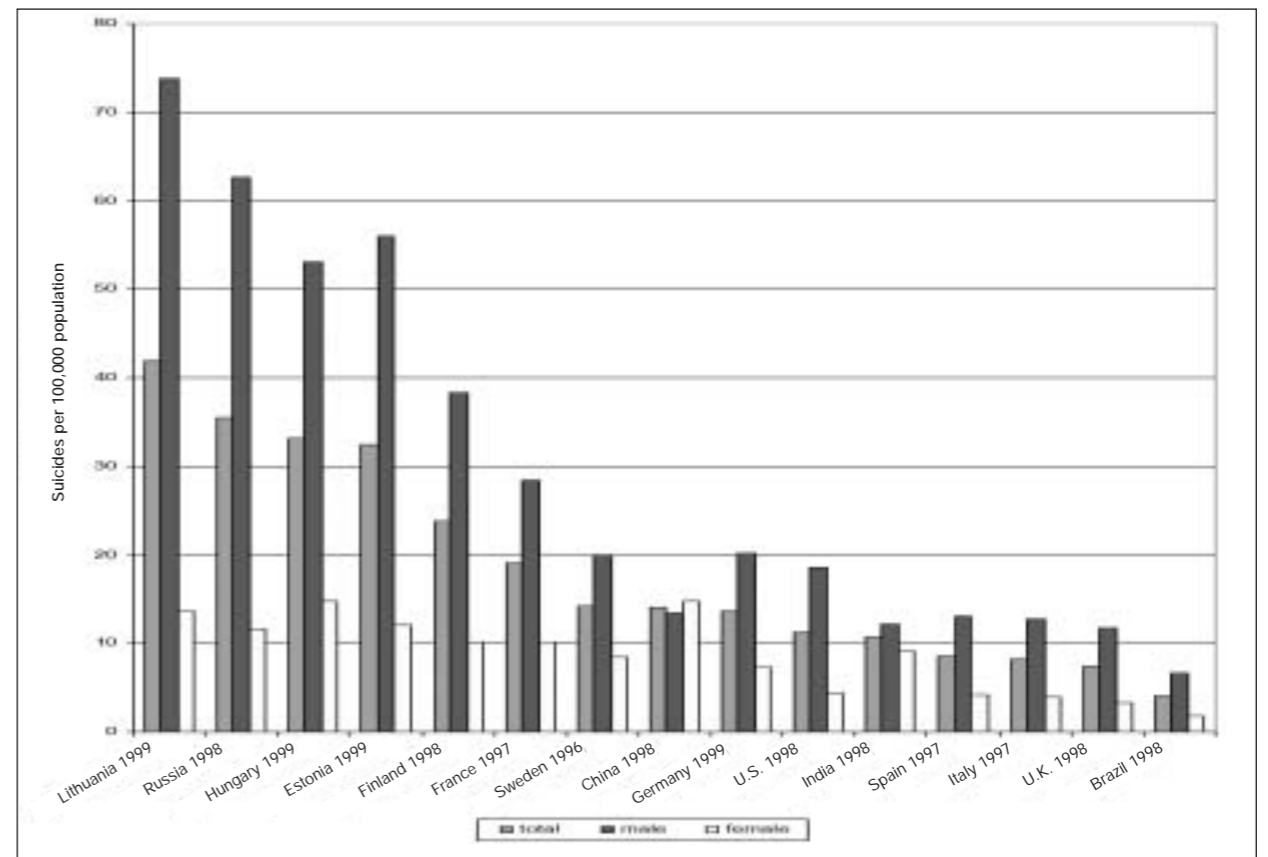


Figure 1 Male and female suicide rates of selected countries

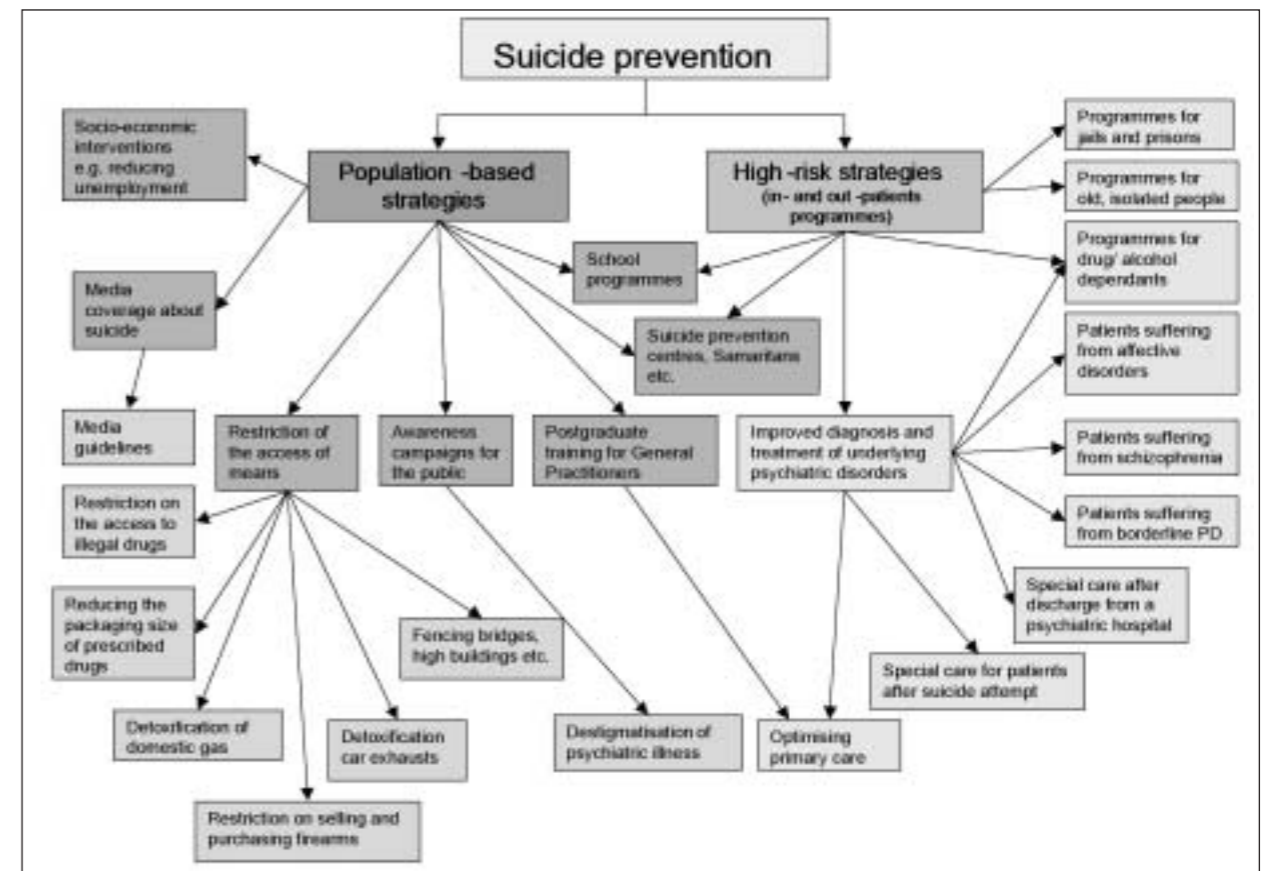


Figure 2 Suicide prevention strategies: an overview

Table 1  
Selected studies which investigated changes in suicidality after specific interventions

	year	subject	methods	results	appraisal
Bagley	1968	Impact of Samaritans on the suicide rate in the UK.	Comparison of the first 15 county boroughs having Samaritan branches and matched control towns.	Significant differences between both groups.	No experimental design. Criteria for the selection of controls questionable.
Kreitmann	1976	Effect of the detoxification of domestic gas on the suicide rate in England and Wales.	Analysis of the course of the suicide rates before and after detoxification of domestic gas.	20% decrease of the suicide rate in England and Wales.	No experimental design. Other variables might have influenced the outcome.
Jennings et al.	1978	Impact of Samaritans on the suicide rate in the UK.	Replication of the study of Bagley (1968). Different method to choose matched controls was established.	No statistically significant differences between Samaritan and control towns.	No experimental design. Criteria for the selection of controls questionable.
Motto et al.	1976 1981	Communication for patients after suicide attempt as a suicide prevention programme.	Randomisation of patients after suicide attempt. Persons in the experimental group were contacted by letter at least four times a year for five years; survival analysis.	During the first two year significantly less During the first two year significantly less x(1.7% versus 3.5%, p=0.043). Afterwards differences slowly faded out.	Encouraging short-term effects. Replication is necessary.
Schmidtko and Haefner	1986	Effects of suicide cases in television movies.	A 6 episode TV-series titled "Death of a student" showed the railway suicide of a young man. Analysis of railway suicides before and after broadcasting.	Significantly more railway suicides in the period after broadcasting in comparison to the previous year.	No experimental design. Difficult to say whether only changes in time and method have taken place.
Rutz et al.	1989	Frequency of suicide on Gotland after systematic postgraduate education of general practitioners.	Two training days within one year. Subject: diagnosis and treatment of depressive disorders. Over 90% of Gotland's GPs took part. Pre/Post comparison of the suicide rates.	Reduction of yearly suicides from 14 cases to 4 cases (p= 0.02). Two years after termination of the programme increase in suicide rate.	Investigated region was quite small (small number of cases); no control; no successful replication so far.
Salkovskis et al.	1990	Evaluation of the efficacy of cognitive behavioural problem solving in patients after suicide attempt.	Randomisation of 22 patients.	Significantly fewer suicides attempts in the problem solving group in the six months follow-up (p=0.049); no differences in the 12 months follow-up.	Small sample. Long-term-effects have not been shown. Replication is necessary.
Coppen et al.	1991	Does lithium reduce the mortality of recurrent mood disorders?	103 patients under lithium treatment were followed up to 11 years. Comparison of mortality with age adjusted rates of the general population.	Mortality under lithium not higher than in the general population; no suicides within the lithium group.	No experimental design; small sample; no control.
Müller-Oerlinghausen et al.	1992	Suicides and para-suicides in a high risk patient group on and off lithium long term medication.	68 Patients, 8 years follow-up, comparison of suicidality under lithium treatment and after discontinuation.	Under lithium treatment (n=55) only one suicide. After discontinuation (n=13) 11 suicides or para-suicides.	No experimental design; encouraging outcome but no control of non-specific treatment effects.
Lester	1993	The effectiveness of suicide prevention centres in the U.S.	Correlation of the presence of suicide prevention centres with changes in the suicide rate from 1970 to 1980 in the USA; multiple regression.	Results indicate a preventive effect of suicide prevention centres. This effect is considered to be weak.	Original approach. Unclear which elements of the suicide prevention centres accounted for the success.
Morgan et al.	1993	Crisis telephone consultation for deliberate self-harm patients.	Randomisation of 212 patients after suicide attempt. Patients in the green-card-group were offered rapid, easy access to psychiatrists in the event of a new crisis.	Strong trend (p=0.053) to reduced suicidal behaviour in the contact group. No differences in the replication some years later.	Small sample. Long term effect unclear.
Sonneck et al.	1994	Imitative suicide on the Viennese subway.	Development of media guidelines; agreement with local media to abstain from reporting on cases of suicide. Pre/post analysis of the suicide rate.	After termination of dramatic press coverage of subway suicides significant decrease of subway-suicides.	Naturalistic design; no control; switch to other methods of suicide remains uncertain.
Shearin and Linehan	1994	Anti-suicidal efficacy of Dialectical Behaviour Therapy (DBT).	Randomisation of 44 females with a recent para-suicide and a diagnosis of borderline personality disorder (BPD).	Significantly less suicides during DBT and in the 6-months follow-up. No differences in the 12 months follow-up.	Small sample; no long-term effects; replication is necessary.
Meltzer and Okayli	1995	The anti-suicidal effect of clozapine in neuroleptic-resistant patients with schizophrenia or schizo-affective disorder.	Pre-post comparison (n=88) of suicidality before and under Clozapine-treatment.	Under clozapine markedly less suicidality; the number of very risky suicide attempts decreased from five to zero.	No experimental design; no control; Other variables might have influenced the outcome
De Leo et al.	1995	Impact on suicidal behaviour of a telephone service designed to provide elderly people with home assistance.	N=12135, Tele-help allowed to call for support at any time. In Tele-Check the client is contacted about twice a week for assessment of needs. Analysis of suicide rates.	less suicidality during intervention when compared to the expected number for the general population (1 instead of 7 suicides).	Naturalistic design; no control; other variables might have influenced the outcome.
Evans et al.	1999	Crisis telephone consultation for deliberate self-harm patients (DHS patients).	Replication of the Study of Morgan et al. (1993). 827 DSH were randomly allocated to either control or intervention (green card) groups.	The intervention had no significant effect on the overall DSH repetition rate. Sub-analysis indicates that first-timers appear to benefit.	Conclusions concerning sub-groups must be regarded as speculative.

suicide. Affective disorders accounted for 30-88% of all cases (Overview: Lonnqvist 2000). Additional risk factors are old age, a history of previous suicide attempt, lack of social support, critical life events, acute crisis, drug and alcohol abuse and chronic physical complaints. The suicide risk for males is 3-5 times higher than the risk for women. In contrast, suicide attempts were found to be most frequent among young females (Schmidtko et al. 1996). As psychiatric disorders are regarded as the most important underlying cause of suicidal behaviour, optimising medical and psychosocial care for people suffering from a psychiatric disorder is often considered to be crucial for successful suicide prevention (Wasserman 2000).

#### • Pharmacological Treatment *Antidepressants*

Antidepressants proved to be effective in the treatment of depressive disorders. Although several studies had shown a relationship between suicidality and low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the spinal cord (Asberg 1997) a direct anti-suicidal effect of antidepressants, which could be expected especially for serotonin-agonistic antidepressants such as SSRI, could not be shown. But there are indirect hints for the suicide-preventative effect of antidepressants. Although depressive disorders are the most important reason for suicide, studies carried out in the U.S. and Sweden showed that only 12 to 16 per cent of suicide victims were treated with antidepressants (Isacsson et al. 1994, 1999). In a study by Isacsson and colleagues (1996) the authors assume that improved treatment of depression with antidepressant medication would cut the suicide rate in Sweden by up to half. The so-called "Gotland Study" (Rutz et al. 1989 a,b) indicated that continuous medical education for general practitioners on depression is able to influence psychopharmacological prescription profiles. In this study, more antidepressant prescriptions were accompanied by a significant reduction of suicidality. But caution should be exercised when generalizing the results because of the lack of a control group, the small sample size and the specific community structure of Gotland. The results of Khan et al. (2000) question an anti-suicidal effect of antidepressants. Using the Food and Drug Administration database they assessed suicides, suicide attempts, and depressive symptom reduction in studies of seven new antidepressants. Among 19,639 participating patients, 34 committed suicide (0.8% per year), and 130 attempted suicide (2.9% per year). Rates of suicide and attempted suicide did not differ significantly among the placebo- and drug-treated groups. The authors themselves pointed out that it is very difficult to interpret these findings, because the analysed trials were not designed to test the anti-suicidal effect of

antidepressants. In addition the patients in antidepressant clinical trials are a highly selected group, not representative of the general population of depressed patients. In general they are not actively suicidal and they are free of co-morbid physical or psychiatric illness (Khan et al. 2000). Moreover, within this analysis it was not possible to quantify the effect of patients who terminated clinical trials prematurely. It is therefore impossible to evaluate the suicide prevention effect of antidepressants by this study. The interim hypothesis that antidepressants might have a detrimental effect, even increasing suicidality (Teicher et al. 1990), was not confirmed (Möller 1992).

#### *Lithium*

There are some indications that long-term treatment with lithium leads to a reduced suicide risk (Coppen et al. 1991; Müller-Oerlinghausen et al. 1992, 1994; Ahrens et al. 1995; Bocchetta 1998). This is largely attributed to lithium's serotonin-antagonistic impact. Several studies showed that patients under lithium treatment had a considerably lower suicide risk than patients who terminated such a treatment prematurely. Mortality during long-term lithium treatment was not higher than in the general population (Müller-Oerlinghausen et al. 1992; Coppen et al. 1991). In a study by Modestin and Schwarzenbach (1992) patients suffering from an affective disorder who were treated with lithium had a lower suicide risk when compared to a matched (not randomised) control group without long-term lithium treatment. Bocchetta et al. (1998) pursued the cases of 100 patients, who received lithium treatment after a suicide attempt. Outcome was analysed in terms of attempted or completed suicide after a mean of 10 years since admission to the lithium clinics. 10 out of 100 committed suicide; 9 out of 10 suicide victims had terminated the treatment prematurely. Suicide risk was 24 times higher during periods off compared with periods on adequate lithium prophylaxis.

This increased suicide risk after the termination of lithium treatment (Baldessarini et al. 1999) could partly be due to rebound effects. The positive findings are therefore difficult to interpret and might reflect an artefact to some degree. Moreover, the encouraging results may not only be due to lithium treatment but also to other non-specific treatment effects. In the studies described, lithium was not randomly allocated, and it is possible that patients who are compliant with lithium and who attend regular consultations are a selected group who might be less likely to show suicidal behaviour.

#### *Neuroleptics*

There are only few studies about the suicide prevention effect of neuroleptics. In an (uncontrolled) pre-post-comparison by Meltzer and Okayli (1995) prior suicidality was assessed

in neuroleptic resistant patients with schizophrenia or schizoaffective disorder. Of these, 88 were treated with clozapine and prospectively evaluated for suicidality. Clozapine treatment during the follow-up period resulted in markedly less suicidality, and the number of very risky suicide attempts decreased from five to zero. The results suggest that the medication might have had a specific antisuicidal effect. Walker et al. (1997) investigated the data of 67,072 patients who were treated with clozapine at that point or in the past to assess effects on mortality. The suicide risk for patients with clozapine was 83% lower when compared to those individuals who had interrupted the treatment. But again, the interpretation of these findings is difficult because there was no randomisation and no control group, and therefore other variables might have influenced the outcome. Recently Khan et al. (2001) examined symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials. The database comprised 10,118 participating patients. Rates of suicide and attempted suicide did not differ significantly between placebo-treated and drug-treated groups. There were no differences between traditional antipsychotics and new antipsychotics. However, the limitations of this study are the same as described above for the investigation of the effects of antidepressants in clinical trials (Khan 2000). In their recent review Tondo and colleagues (2001) came to the conclusion that an anti-suicidal effect of antipsychotics remains uncertain.

#### • Psychological and psychosocial strategies *Psychotherapeutic approaches*

Studies which report outcomes of randomised, controlled psychotherapy trials, focusing on patients with a history of deliberate self-harm behaviour, are sparse. Only very few of them report significantly better results in terms of less repetition of deliberate self-harm. The interpretation of the results is difficult due to the small sample size in many of the studies. Shearin and Linehan (1994) evaluated the efficacy of dialectical behaviour therapy in 24 females with a recent parasuicide and a diagnosis of borderline personality disorder. Compared to a control group (n=23) there were fewer parasuicides during therapy. In the six months follow-up these results could be confirmed, but after another year there were no significant differences between these groups. Salkovskis (1990) carried out a randomised controlled trial to evaluate the efficacy of cognitive behavioural problem solving in patients after suicide attempt (n=22). Six months after treatment the frequency of attempted suicide was reduced compared to the control group. These differences vanished one year after the treatment.

*Help-lines and Community Support Programmes*  
Crisis intervention centres and their role in suicide prevention were evaluated in a study carried out in the United Kingdom. The role of the Samaritans in suicide prevention remains controversial because the findings only lead to ambiguous conclusions (see Table 1; Bagley 1968; Jennings et al. 1978). When evaluating the effects of suicide prevention centres in the U.S., Lester (1993) was able to show significant, but still very small effects on the suicide rate. A replication of these results in Canada was not successful. The influence of crisis intervention centres on the suicide rate therefore has to be regarded as moderate at best.

Motto et al. (1976) randomised patients after suicide attempt, contacting one group on a regular basis. Persons in the experimental group were contacted by letter at least four times a year for five years, while the patients in the other group were not actively contacted. Patients in the contact group had a lower suicide rate during all five years of the study. Differences in the rates gradually diminished after the program was terminated (Motto et al. 1981).

Morgan et al. (1993) randomized 212 patients after suicide attempt. Patients who had harmed themselves for the first time were offered rapid, easy access to on-call trainee psychiatrists in the event of further difficulties, and they were encouraged to seek help at an early stage should such problems arise. When comparing the suicidality in both groups there was a trend (p=0.053) for less suicidal behaviour in the experimental group. A replication did not confirm this outcome and showed no differences between the two groups (Evans et al 1999).

De Leo et al. (1995) investigated the impact on suicidal behaviour of Tele-Help/Tele-Check, a telephone service designed to provide 12,135 elderly people with home assistance. Tele-help allowed a call for support at any time. In Tele-Check the client is contacted about twice a week for assessment of needs and for emotional support. This uncontrolled study found less suicidality during intervention when compared to the expected number for the general population (one instead of seven suicides).

#### Population-based strategies

Population-based strategies are defined as programs that focus first on the population as a whole, not specifically targeting people at risk.

#### • Restriction of the access to means

There is no doubt that reducing the availability of a method for suicide reduces its use for suicide. Kreitman's "coal-gas study" is legendary regarding that aspect. The author was able to show that although joblessness was on the rise in England during the 1960s the detoxification

of domestic gas led to fewer suicides during that time period. But there is considerable debate about the middle- and long-term effects of such strategies. Some authors suggest that suicidal persons might switch to other methods, but empirical findings confirm at least short- and middle-term effects. Kreitman (1976) and Lester (1998) supposed that the restriction of access might have a special suicide prevention effect if the method itself had been regarded to be common and fatal in the past.

Medication overdose is the most important method of intentional poisoning. Henry et al. (1995) showed that older tricyclic antidepressants (TCAs) like amitriptyline and dothiepin are highly toxic in overdose in comparison to SSRIs. Between 1987 and 1992 TCA-overdose accounted for 1,563 suicides in Great Britain. Besides the inherent toxicity of the drug, prescribing practices seem to play an important role. A switch to prescribing less toxic drugs and restricting the quantity of drugs available as a single purchase could reduce the number of deaths from overdose.

#### • Media coverage of suicide

Several studies underline the effect of media coverage of suicide on imitation (Phillips 1974). Both the fictional and non-fictional coverage of individual suicide cases in newspapers, magazines, television and radio can serve as a role model and might lead to imitation effects. Phillips (1974) showed that the more publicity a suicide case was given, the more suicides were found in the period following publication. This finding could be replicated in many other studies (Overview: Schmidtke 2000). Schmidtke and Hafner (1986) used a natural single case experiment to prove an imitation effect. A six episode TV-series entitled "Death of a student" showed the railway suicide of a 19-year old male student. In five of six episodes the scene of the suicide was shown at the beginning of the movie. After the broadcasts, an increase in railway suicides was found over several weeks. This was especially true for the age- and sex-group which closely resembled the model. The authors argued that the suicide of the young student in the movie prompted other youths to commit suicide. Some studies showed that the absence of mass media reports of suicide might contribute to suicide prevention. Sonneck and colleagues (1994) showed that the number of subway suicides in Vienna decreased after a change in the newspaper coverage about these suicide cases. The media were informed about the negative effect of emotional coverage about subway suicides. When the sensational and dramatic way of portraying these suicides ceased, the number of persons using this method reduced significantly.

Although there is no doubt that an imitation effect exists, it is difficult to say whether only

changes in time and method have taken place. There are some theoretical justifications to suppose that imitation effects lead to additional suicides, but it is difficult to prove this hypothesis.

#### • Optimisation of primary care

Depression has to be regarded as one of the most important risk factors for suicides (Lonnqvist 2000). Epidemiological data show a lifetime prevalence of 13-20% for depressive illness in the developed countries (Kessler et al. 1994; Wittchen et al. 1992). Half of the individuals affected consult a general practitioner. But depression is often overlooked, and very few patients receive sufficient antidepressive medication (Lepine et al. 1997). Only 24% of the victims had had contact with mental health services in the year before death (Appleby et al. 1999); on the other hand, 40% of suicide victims were seen by a general practitioner in the four weeks before their death (Vassilas and Morgan 1993). If it were possible correctly to identify at least some of those at risk a reduction of suicidality would be possible. This was suggested by the findings of the previously mentioned Gotland study, which showed lower suicide rates after postgraduate training of general practitioners on how to recognize and treat depression (Rutz et al. 1989 a,b).

The importance attributed to primary care in suicide prevention differs, however. Callahan et al. (1994) examined the effect of screening and specific therapy guidelines for general practitioners (n=103) on the therapy of depression among the elderly in a randomised and controlled study. Although depression was more often diagnosed and antidepressants were more often prescribed when compared to a control group (treatment as usual) the depression scores (HAM-D) in both groups did not differ significantly at any point during the examined period of nine months. These findings are supported by a recent study by Thompson et al. (2000), where general practices had received training on the diagnosis and therapy of depression (four-hour training) in a controlled and randomised study with a total sample size of 60 practices. Those practices which had received training did not diagnose depressive disorders more often than practices in the control group, and there were no differences in clinical improvement between the groups. The authors therefore came to the conclusion that educational programs in primary care are unlikely to reduce suicidality.

#### • Information campaigns and educational programmes

Prejudice and a lack of information among the general public about affective disorders interfere with progress in recognition and treatment of depression (Paykel et al. 1997). Public opinion, but very often also the patients themselves, do

not regard depression as an illness but as a personal fault and disability. There is especially ignorance concerning the pharmacological treatment of depression. In Great Britain a public information strategy was started to increase understanding and reduce stigma, including a five-year 'Defeat Depression' campaign. Media reports, information leaflets, books and self-help videos informed about symptoms, causes and the treatment of depressive disorders. Particular attention was paid to updating general practitioners in the recognition, detection and management of depression. The goal was to decrease suicidality by 15% until the year 2000 (Paykel et al. 1998). To evaluate the activities, surveys of public attitudes were conducted in late 1991, early 1995 and mid-1997 (Paykel et al. 1997; Rix et al. 1999). Each covered approximately 2,000 subjects, sampled to be representative of the population of Great Britain. The authors showed that there was a significant increase in knowledge about biological causes and the understanding of depression. Sixty percent of those questioned after five years of intervention regarded medication as a successful treatment of depression compared to 46% before the start of the campaign. But the campaign was not able to influence views about the supposed addictiveness of antidepressants in a substantial way. Seventy-four percent (versus 78% before the start of the campaign) still believed that antidepressants were addictive. The overall suicide rate fell by 11.7% in five years. There are some doubts whether the campaign itself or non-specific factors contributed to the increase in knowledge. Whether the campaign had an influence on the care of depression (diagnoses, prescription profiles, referrals to specialists) and the decrease of the suicide rate, remains uncertain due to the study design (no control).

#### • Socio-economic factors

Durkheim (1973) put forward the hypothesis that suicidality is influenced by society, its stability and the ability to form attachments and relationships. This hypothesis has been discussed for the last 100 years, but studies could not conclusively link crises in society to an increase in suicidality. Eastern Germany seems to be a good example of a negative correlation. Although the country underwent severe societal change, and unemployment rose to more than 25%, suicidality decreased. Predictions that societies with greater economic wealth and individual prosperity would be affected by a rise in suicidality could not be proved. On the contrary, economic prosperity correlated positively with low suicide rates (Ferrada Noli 1997; Lewis et al. 1997) although a direct chronological correlation between prosperity and suicidality could not be proved for Germany (Hafner 1998).

Unemployed persons are over-represented

among suicide victims (Platt 1984; Lewis and Sloggett 1998). Lewis and colleagues (1997) even consider socio-economic measures that target unemployment to have a stronger anti-suicidal effect than any high-risk strategies. Most studies were able to show that there is a positive relationship between unemployment and suicidality but the interaction between the two factors remains unclear and hypothetical. Platt suspects that people lose their jobs because they suffered from a psychiatric disorder (selection paradigm). This hypothesis is supported by a Danish study investigating 811 suicides (Mortensen et al. 2000). When statistically controlling the influence of the criterion "psychiatric disorder", only 3% of the variance could be explained by joblessness. But it is possible that unemployment in psychiatric patients might influence vulnerability. The lack of a protective factor (e.g. employment) could increase the suicide risk.

#### Discussion

Most studies described in this review could not prove the efficacy of suicide prevention activities. This is true for high-risk strategies as well as for population-based strategies. Methodological problems and shortcomings are the main reasons for the lack of knowledge. The possible influence of unspecific variables and the absence of control and randomisation impair the impact of the studies. The interpretation of the data is difficult due to small sample sizes. Statistical power is in most cases so weak that significant results are unlikely. Lewis et al. (1997) pointed out that a sample size of about 20,000 people would be necessary to evaluate the effects of high-risk strategies (assuming  $p=0.05$ ; 25% reduction in rates and 80% power).

In the last 30 years suicide rates world-wide have not decreased although the use of psychotropic drugs has become increasingly common. Still, there are some pharmacological interventions which seem to be successful in suicide prevention. One of them is lithium prophylaxis for patients suffering from affective disorders. In contrast it is difficult to prove a specific suicide prevention effect of antidepressants. Such an effect is probable, but has not been proved by studies so far. There are also not enough data to confirm an anti-suicidal effect of antipsychotics. When looking at psychotherapy and its potential anti-suicidal impact, the data are too weak to come to safe conclusions. Therefore the relevance of high-risk strategies for suicide prevention has to be questioned in principle (Lewis et al. 1997).

Most individuals who would be identified as members of high-risk groups will never come into contact with public health care institutions. They avoid psychiatric institutions or

withdraw from psychotherapeutic and pharmacotherapeutic interventions. High-risk strategies are therefore subject to the risk of reaching out to only a very small minority in the community. Hence it is doubtful that high-risk strategies alone will contribute much to a decrease of the overall suicide rate. In order to reach more people at risk, suicide prevention measures have to get in touch with individuals in their normal, everyday environment, at places where they usually try to get support. Therefore the focus should be on primary care. Seventy to eighty percent of the population contact their general practitioner on a regular basis. General practitioners play a key role because it is mostly up to them whether a depressed and suicidal person is identified and correctly treated or not. In order to make use of the preventative impact of medication and therapy, diagnosis and treatment in primary care would have to be improved. But optimisation of primary care is not so easy. The findings of some studies question the assumption that short-time training can qualify GPs to diagnose and treat depression correctly. Prejudices, fears and a lack of information in the public about depression also contribute to the current difficult situation. Global preconceptions about psychotropic drugs and fear of stigmatisation prevent patients from seeking psychiatric help. Therefore information for the public is crucial for the optimisation of primary care and the success of suicide prevention. The data suggest that no single method on its own can substantially tackle a complex problem such as the care of depressed patients and the reduction of suicidality. When reviewing the studies that are available, a multi-level approach that tries to integrate different interventions (high-risk and population based strategies) is the most promising. Such an approach should include measures 1) to optimise the treatment of psychiatric disorders; 2) to inform the public about this topic; 3) to provide special offers for high-risk groups; and 4) recommendations for the media on how to prevent imitation effects when covering suicides. Strong synergistic effects can be expected from such a diversified approach. Better-informed patients meet with more qualified GPs in primary care, and both sides can form a patient-doctor alliance against depression.

In 2001 the nation-wide Research Network on Depression and Suicidality (funded by the German Ministry for Research and Education) implemented a special suicide prevention action programme in Nuremberg in Germany. This programme combines the different approaches mentioned above. In order to increase the power of the study, the total number of suicidal acts (suicides and parasuicides) in Nuremberg (480,000 inhabitants) was chosen to be the main criterion for the evaluation. The effects

will be evaluated with respect to a one-year baseline and a control region (Wuerzburg, 270,000 inhabitants). In addition, variations in the prescription profiles of physicians and in the number of referrals to specialists will be analysed. Possible changes in public attitudes towards depression and pharmacological treatment will be evaluated by representative telephone surveys (pre/post).

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## Bipolar II Disorder and Major Depressive Disorder: Continuity or Discontinuity?

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### Summary

**Aim:** To find if bipolar II disorder (BPII) and major depressive disorder (MDD) were distinct categories or overlapping syndromes.

**Methods:** 308 BPII and 236 MDD outpatients, presenting for major depressive episode (MDE) treatment, were interviewed with the Structured Clinical Interview for DSM-IV. History of mania and hypomania, and hypomanic symptoms present during MDE, were systematically investigated. Presence of zones of rarity between BPII and MDD depressive syndromes was assessed. Atypical and hypomanic symptoms were chosen because atypical features and depressive mixed state (ie, MDE plus more than 2 concurrent hypomanic symptoms, according to Akiskal and Benazzi 2003) were often reported to distinguish BPII from MDD depressive syndromes (more common in BPII). If BPII were a distinct category, distributions of these symptoms should show zones of rarity between BPII and MDD depressive syndromes. Histograms and Kernel density estimate were used to study distributions of these symptoms.

**Results:** BPII had significantly more atypical features and depressive mixed state than MDD. Histograms and Kernel density estimate curves of distributions of atypical and hypomanic symptoms in the entire sample did not show zones of rarity.

**Conclusions:** Finding no zones of rarity supports a continuity between BPII and MDD (meaning partly overlapping disorders without clear boundaries).

**Key words:** bipolar II disorder, major depressive disorder, bipolar spectrum, category, classification.

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### Introduction

It is not yet clear if mood disorders are distinct categories, as classified by DSM-IV-TR (American Psychiatric Association 2000) and ICD-10 (World Health Organization 1992), or a spectrum of overlapping disorders (Akiskal 2003). Usual diagnostic validators are family history, diagnostic stability, age of onset, clinical features, gender, co-morbidity, personality, treatment response, outcome, biology and statistical techniques (Kraepelin 1921; Robins and Guze 1970; Kendler 1990; Angst and Gamma 2002; Akiskal 2003; Kendell and Jablensky 2003; Kendler et al. 1996). Some data support a categorical approach because of differences in diagnostic validators (Winokur et al. 1993 a,b, 1995; Kendler et al. 1996; Sato et al. 2002; Quitkin et al. 1993; Coryell 1999; McMahon et al. 1994, 2001; Coryell et al. 1995; Clayton et al. 1992; Andreasen and Grove 1982). Some data support a dimensional (continuity) approach because of similarities in diagnostic validators (Kendler and Gardner 1998; Angst et al. 2000; Judd et al. 1998, 2002, 2003 a,b; Goodwin and Jamison 1990; Akiskal 2002; Judd and Akiskal 2003; Kelsoe 2003; Akiskal et al. 1983, 1995; Angst et al. 2003; Ghaemi et al. 2002; Cassano et al. 1992; Akiskal et al. 2003 a,b,c; Akiskal et al. 1983).

According to Kendell and Jablensky (2003), finding a bimodal distribution (zone of rarity) of some distinguishing cross-sectional symptoms between two related syndromes would support a categorical approach. Bipolar II disorder (BPII) is the closest of the bipolar disorders to unipolar major depressive disorder (MDD), and it could be the one to compare to MDD. The cross-sectional symptoms to study should be those that most distinguish the two depressive syndromes. In the comparison of major depressive episode (MDE) in BPII and MDD, atypical features and depressive mixed state [MDE plus more than two concurrent hypomanic symptoms (Akiskal and Benazzi 2003)] were often reported to be much more common in BPII (Angst et al. 2002; Benazzi 2000a; Akiskal 2002, 1996; Goodwin and Jamison 1990; Hantouche et al. 1998; Ghaemi et al. 2002). Finding zones of rarity in the distribution of atypical and hypomanic symptoms could support a categorical approach.

**Study aim:** To find if BPII and MDD were distinct categories or overlapping disorders along a continuum without clear boundaries.

### Materials and methods

#### • Study setting

A general psychiatry outpatient private practice (a University of California at San Diego (USA) collaborating centre). Private practice is more representative of mood disorders in Italy, because it is the first or second (after family doctors) line of treatment of mood disorders, because psychiatric patients often prefer to be treated outside the national mental health service (NHS), and because the most severe patients are usually seen in the NHS and in the university. Almost all individuals can be visited by a private psychiatrist because the fee is not high (reducing a possible bias related to income).

#### • Interviewer

A senior clinical (20 years in practice) and mood disorder research psychiatrist.

#### • Patients

Consecutive 308 BPII and 236 MDD outpatients, presenting spontaneously for MDE treatment were included in the last 4 years (intake sample features are presented in Table 1), who were off psychoactive drugs for at least two weeks, to avoid inclusion of antidepressant-induced mixed states (Akiskal and Pinto 1999). Substance-related and borderline personality disorders were excluded, because they may confound the diagnosis of BPII (Akiskal and Pinto 1999), and are rare in the study setting (Benazzi 2000b). Clinically significant general medical illnesses and cognitive disorders were also excluded. Part of this sample was included in previous studies on depressive mixed states, as the study of depressive mixed states is an ongoing project.

#### • Interview method

The Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First et al. 1997), as modified by Benazzi and Akiskal (2003), was used during the first visit assessment. Diagnosis of borderline personality disorder was done following a semi-structured interview based on DSM-IV criteria [prevalence of borderline personality disorder was found to be low with SCID-Axis II interviewing in the study setting (Benazzi 2000b)]. The SCID-CV is a partly semi-structured interview based on clinical evaluation (not on simple yes/no answers to structured questions). Wording of the questions can be changed to improve/check understanding. To improve detection of hypomanic symptoms during MDE the Hypomania Interview Guide (HIG), Current Assessment Version (Williams et al. 1994, 2000), was used. More details on methods can be found in Akiskal and Benazzi (2003) and Benazzi and Akiskal (2003).

#### • Diagnosis of history of hypomania

History of mania and hypomania was systematically investigated soon after the diagnosis of MDE, to avoid a possible bias related to knowledge of bipolar signs. Probing was more focused on history of overactivity (increased goal-directed activity) than mood change, as suggested by Akiskal et al. (1977), Angst et al. (2003), and Benazzi and Akiskal (2003). DSM-IV 4-days minimum duration of hypomania for BPII diagnosis was not followed, because this cut-off was not based on data (Dunner 1998). Instead, at least two days of hypomania were required, following previous reports (Judd et al. 2003b; Angst et al. 2003; Cassano et al. 1992; Coryell et al. 1995; Akiskal et al. 1995, 2000; Akiskal 1996; Benazzi 2001; Simpson et al. 2002). The SCID-CV structured question on racing thoughts was supplemented by Koukopoulos and Koukopoulos' definition

Table 1

Features of the bipolar II (BPII) and major depressive disorder (MDD) sample at intake (n=544)

Variables: mean (SD), %	BPII n=308	MDD n=236	T/Z	DF	P
Female gender	67.8	60.5	1.7		0.0776
Index age, years	41.7 (13.5)	46.8 (15.0)	-4.1	542	0.0000
Age of onset of the first MDE	22.8 (10.7)	31.9 (14.1)	-8.5	542	0.0000
>4 MDEs	80.5	58.4	5.6		0.0000
MDE symptoms >2 years	41.8	35.5	1.4		0.1355
Axis I comorbidity	53.5	45.7	1.8		0.0713
Index MDE GAF score	50.6 (9.1)	51.0 (9.4)	-0.5	542	0.6167
Index Hypomania Interview Guide score	8.3 (3.6)	5.6 (3.6)	8.6	542	0.0000
Index MDE with atypical features	54.5	29.6	5.8		0.0000
Index MDE with melancholic features	12.0	14.4	-0.8		0.4100
Index MDE with psychotic features	8.1	8.0	0.0		0.9661
Index Depressive Mixed State	62.0	32.2	6.8		0.0000
Bipolar (type I+II) family history	51.2	18.1	7.9		0.0000

(MDE=major depressive episode; GAF=global assessment of functioning scale)

(1999) of crowded thoughts (i.e. head continuously full of ideas the patient is unable to stop). Family members and close friends, often present during the interview, supplemented clinical information [increasing BPII reliability (Akiskal et al. 2000; American Psychiatric Association 2000)]. Most BPII had had more than one hypomania [increasing BPII reliability (Akiskal et al. 2000)].

- Reliability and validity of BPII diagnosis

The SCID-CV inter-rater reliability kappa is 0.70-1.0 (First et al. 1997), the interviewer's inter-rater reliability kappa is 0.73 (Benazzi In Press). BPII versus MDD had typical differences (Table 1) (onset, recurrences, atypical depression, bipolar family history) (Angst et al. 2003; Goodwin and Jamison 1990; McMahon et al. 1994; Coryell 1999; Benazzi 2000a; Akiskal and Benazzi 2003).

- Family history

Bipolar (type I and type II) family history was investigated with the Family History Screen (Weissman et al. 2000), a structured interview for psychiatric history of first-degree relatives, by interviewing the patient and often also one first-degree relative.

- Testing study aim

To find if BPII and MDD were distinct categories with clear boundaries or were partly overlapping syndromes along a continuum, the Kendell and Jablensky (2003) method was followed, by looking for zones of rarity between some cross-sectional features of the two related depressive syndromes (MDE in BPII versus MDD). To test if a zone of rarity (or bimodality) was present, the distributions of DSM-IV-TR atypical and hypomanic symptom numbers in the MDEs of BPII versus MDD were studied. Atypical symptoms and hypomanic symptoms (present during the MDE) were chosen because the atypical features specifier and depressive mixed state were cross-sectional features often reported to distinguish BPII and MDD depressive syndromes (much more common in BPII MDE versus MDD) (Akiskal and Benazzi 2003; Akiskal 2002; Goodwin and Jamison 1990; Baldessarini 2000; Perugi et al. 1998; Angst 1996; Angst et al. 2002). If BPII were a category distinct from MDD, the distributions of these symptoms should show a zone of rarity between the two depressive syndromes.

- Statistics

Means were compared by the t-test, proportions were compared by the two-sample test of proportions. Histograms and univariate Kernel density estimate were used to study symptom distributions. Kernel density estimate evaluates multimodality better than the histogram (Salgado-Ugarte et al. 1994). STATA Statistical

Software, Release 7, was used (Stata Corporation, College Station, TX, USA, 2001). P values were two-tailed, and alpha level was set at 0.05.

## Results

Comparisons between BPII and MDD are presented in Table 1. BPII patients had significantly lower age, lower age of onset, more recurrences, more depressions with atypical features, more depressions with depressive mixed state, higher severity of the Hypomania Interview Guide, and more bipolar family history. Histograms and Kernel density estimate curves of the distributions of the numbers of atypical and hypomanic symptoms present during the MDE in the entire sample (n=544) are presented in Figures 2-4. No zones of rarity were found.

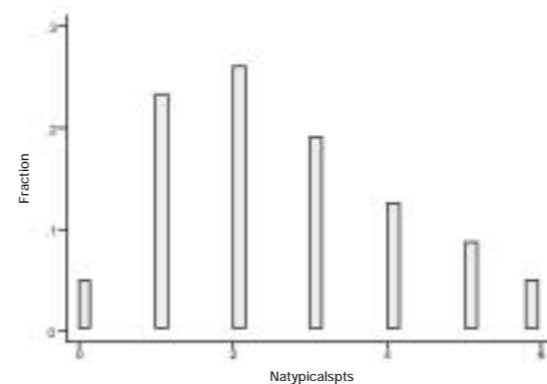


Figure 1  
Histogram of the distribution of the number of atypical features symptoms (Natypicalspts) between bipolar II and major depressive disorder depressive syndromes.

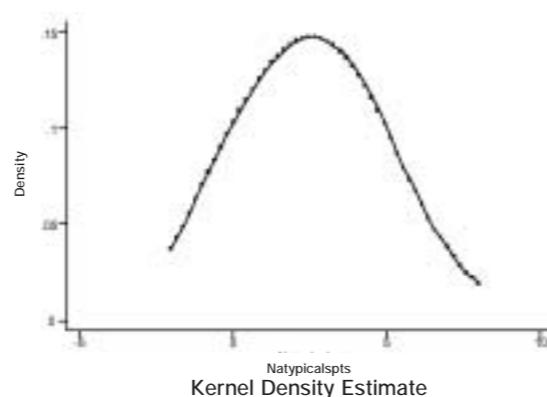


Figure 2  
Kernel density estimate distribution of the number of atypical features symptoms (Natypicalspts) between bipolar II and major depressive disorder depressive syndromes.

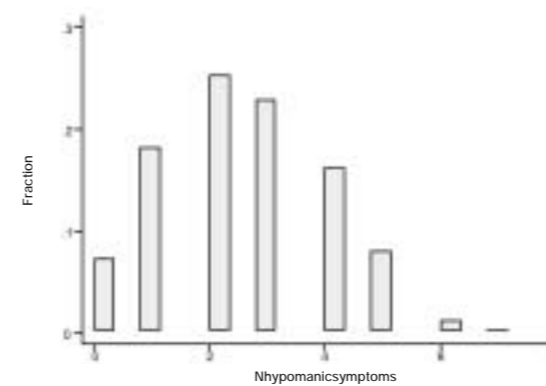


Figure 3  
Histogram of the distribution of the number of hypomanic symptoms (Nhypomanicsymptoms) between bipolar II and major depressive disorder depressive syndromes.

## Discussion

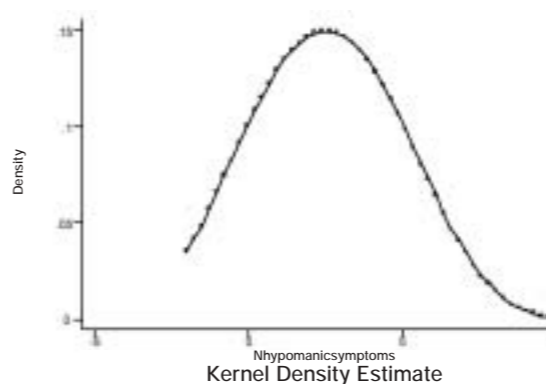


Figure 4  
Kernel density estimate distribution of the number of hypomanic symptoms (Nhypomanicsymptoms) between bipolar II and major depressive disorder depressive syndromes.

Results showed that BPII and MDD had clinical and family history distinguishing features, in line with previous reports (Akiskal 2002; Goodwin and Jamison 1990; Baldessarini 2000; Perugi et al. 1998; Angst 1996; Angst et al. 2002; Hantouche et al. 1998; McMahon et al. 1994; Akiskal and Benazzi 2003; Benazzi 2000a). However, distribution of the number of symptoms of the most distinguishing cross-sectional features (atypical features of depression and depressive mixed state) did not show any zone of rarity between the two depressive syndromes. If the two depressive syndromes had clear boundaries (i.e. were categories), bimodality of the symptoms distributions should have been present. Finding no zone of rarity supports a continuity between BPII and MDD, according to the Kendell and Jablensky (2003) method. This finding is in line with Pages and Dunner (1997), Akiskal (2003), Goodwin and Jamison (1990), and Ghaemi et al. (2002) spectrum view of mood disorders, which includes many MDD subtypes in the manic-depressive illness. Kraepelin (1921) stated about

manic-depressive insanity that "delimitation of individual clinical forms of the malady is in many respects wholly artificial and arbitrary". Recurrent nonbipolar depressions were included, as recurrent attacks more than polarity were the main feature of manic-depressive insanity. Continuity among mood disorders means that mood disorders are partly distinct and overlapping clinical entities, that is, more dimensional than categorical entities, and not simply dimensional entities distinguished by the grading of some variable, like severity (Kelsoe 2003; Akiskal 2003; Goodwin and Jamison 1990). From a family history point of view (one of the most important diagnostic validators), while finding more BPII than bipolar I (BPI) in families of BPII probands, and more BPI than BPII in families of BPI probands could support distinct categories (Coryell 1999), the finding that MDD was the most common mood disorder in both BPI and BPII probands' families (running against the "breeding true") could support a continuity between BP and MDD (Kelsoe 2003).

- Limitations

To use a single interviewer limits the validity of the findings. However, the interviewer had a high inter-rater BPII reliability, and present study BPII had typical bipolar features, supporting the interview validity. Use of a semi-structured interview increased reliability and correct BPII diagnosis. Low BPII diagnostic reliability has been reported (Coryell 1999; Andreasen et al. 1981; Mazure and Gershon 1979; Keller et al. 1981; Rice et al. 1986). Recent studies using semi-structured interviews by clinicians, instead of fully structured interviews by non-clinicians, found many false negatives compared to fully structured interviews (Aalto-Setälä et al. 2002; Eaton et al. 2000; Brugha et al. 1999; Helzer et al. 1985; Dunner and Tay 1993; Simpson et al. 2002; Ghaemi et al. 2002). BPII had high diagnostic stability (Coryell et al. 1995; Akiskal et al. 1995) when diagnosis was done by clinicians using a semi-structured interview. Interview of key informants increased the validity of the BPII diagnosis (American Psychiatric Association 2000; Akiskal et al. 2000). The interviewer had been studying and treating BPII for many years. All consecutive patients had a systematic and standard interview. These study features should have reduced study limitations. However, replication by independent groups and in different settings is required. Recently, Sato et al. (2003) and Judd et al. (2003b) have replicated the interviewer's findings on depressive mixed states, by using different methods and in different settings.

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## Adjunctive Topiramate in Bipolar II Disorder

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### Summary

We evaluated the efficacy and safety of adjunctive topiramate in bipolar II patients who were either treatment-resistant to or unable to tolerate lithium, carbamazepine or valproate. Nineteen DSM-IV bipolar II patients received increasing doses of open-label topiramate as adjunctive therapy for their hypomanic ( $n=15$ ) or depressive ( $n=4$ ) symptoms. Sixteen patients completed the 12-week follow-up. There were highly significant improvements in YMRS, HDRS and CGI-BP-M scores ( $p=0.0001$ ). Of the fifteen hypomanic patients, eight (53%) were rated as responders to topiramate (50% reduction in YMRS scores), and five (33%) met criteria for remission (YMRS score  $\leq 8$ ). Two of the four patients with a depressive episode at study entry (50%) were rated as responders (50% reduction in HDRS score), and one (25%) achieved remission (HDRS score  $\leq 6$ ). Topiramate was generally well tolerated. One third of the patients experienced weight loss. These preliminary results suggest that adjunctive topiramate may be useful in treating bipolar II disorder.

**Key words:** bipolar disorder, mania, mood stabilisers, topiramate.

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### Introduction

Although bipolar II disorder is generally regarded as a milder form of bipolar illness (APA 1994), this is not entirely true, and effective treatments are urgently needed (Vieta et al. 1997). In fact, bipolar II disorder is often associated with poorer clinical outcomes, including a higher risk of suicide, than both bipolar I disorder and unipolar depression (Rihmer and Pestaloty 1999; MacQueen and Young 2001). The traditional anticonvulsants valproate and carbamazepine are now widely used as alternatives or adjuncts to lithium in the treatment of bipolar disorders. The established efficacy of these agents has led to increasing interest in the potential value of newer anticonvulsants to treat bipolar disorder.

Topiramate is a structurally novel anticonvulsant that shares some of the pharmacological properties of valproate and carbamazepine (Shank et al. 2000). Like both valproate and carbamazepine, topiramate inhibits voltage-activated  $\text{Na}^+$  channels (Coulter et al. 1993; De Lorenzo et al. 2000) and, like valproate, topiramate enhances GABA neuroinhibition (White et al. 1997). In addition, topiramate modulates glutamate-mediated neuroexcitation (Skradski and White 2000) and some voltage-activated  $\text{Ca}^{2+}$  channels (Zhang et al. 2000), and inhibits two isoenzymes of carbonic anhydrase (CA-II and CA-IV) at therapeutically relevant concentrations (Dodgson et al. 2000).

Open-label studies of topiramate in more than 800 patients with bipolar disorder suggest that this drug may possess mood-stabilising properties in both mania and depression (Marcotte 1998; Chengappa et al. 1999; McElroy et al. 2000; McIntyre et al. 2002; Bozikas et al. 2001; Calabrese et al. 2001; Ghaemi et al. 2001; Grunze et al. 2001; Valle-Cabrera et al. 2001; Vieta et al. 2001). Each of these studies, enrolling basically bipolar I patients, reported improvement in more than 50% of patients treated with topiramate. However, controlled trials have not supported the short-term efficacy of this drug in monotherapy in acute mania (Calabrese 2000). Thus, the utility of topiramate in non-manic forms of the bipolar illness and in longer-term treatment is still an open question. We have previously suggested that topiramate was effective in bipolar patients, including a

small number of patients with bipolar II disorder (Vieta et al. 2001; 2002a). Based on this initial experience, we decided to conduct a further open-label trial of topiramate in a larger patient population. To the best of our knowledge, this is the first study on topiramate in the treatment of bipolar II disorder.

### Patients and Methods

Nineteen patients fulfilling DSM-IV criteria for bipolar II disorder (hypomanic or depressed episode) entered the study (Table 1). All patients had either poorly responded to or were intolerant of treatment with lithium, carbamazepine or valproate defined as having two mood episodes or more during mood-stabilising therapy and/or unacceptable side-effects. Patients also had Young Mania Rating Scale (YMRS) (Young et al. 1978; Colom et al. 2002) or 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) scores of 12 and Clinical Global Impressions scale - bipolar version modified (CGI-BP-M) (Vieta et al. 2002b) scores of 4 in at least one subscale. The CGI-BP-M is a brief version of the CGI-BP (Spearing et al. 1997) with 3 subscales: one for cross-sectional manic and hypomanic symptoms, another for cross-sectional depressive symptoms, and a third one for long-term outcome. Every subscale ranges from 1 (normal) to 7 (extremely ill). A score of 4 means moderate severity of symptoms. Fifteen patients had hypomanic symptoms and four patients had depressive symptoms. All were intended to be treated for 12 weeks.

Table 1

Patient characteristics (n=19)	
Mean age (range), years	43.2 (22-60)
Gender, n (%)	
Female	14 (74)
Male	5 (26)
Mood state at entry, n (%)	
Hypomanic	15 (79)
Depressed	4 (21)
Psychiatric co-morbidity, n (%)	
Any	13 (68)
Substance abuse	6 (32)
Personality disorder	4 (21)
Anxiety disorder	4 (21)
Eating disorder	2 (11)
Pathological gambling	1 (5)
Suicide attempts	6 (32)
Rapid cyclers	7 (37)

Table 2

Concomitant mood-stabilising treatments	
	n (%)
None	5 (26)
Lithium	6 (32)
Valproate	4 (21)
Carbamazepine	3 (16)
Lamotrigine	3 (16)
Gabapentin	1 (5)

Topiramate was added to existing mood-stabilising treatments at a starting dose of 25-100 mg/day. Doses were typically increased whenever possible by 20-60 mg/day every three to seven days until clinical response or optimal tolerability. The mean starting dose of topiramate was  $61 \pm 53$  mg/day, and mean doses at weeks 2, 4 and 12 were  $121 \pm 128$ ,  $164 \pm 120$  and  $177 \pm 119$  mg/day, respectively. The most commonly prescribed treatment at baseline was lithium ( $n=6$ ) (Table 2). Co-medication remained stable during the observational period. Clinical assessments evaluated at baseline and at weeks two, four and 12 included the YMRS, HDRS, CGI-BP-M and the incidence of side effects. Comparisons between baseline and other measurements were made using the Wilcoxon test (last observation carried forward). All analyses were performed on an intention-to-treat basis.

Response to topiramate was defined as at least 50% reduction in YMRS (hypomanic patients) or HDRS (depressed patients) scores from baseline. Remission was defined as a total YMRS score  $\leq 8$  (hypomanic patients) or HDRS score  $\leq 6$  (depressed patients).

### Results

Sixteen patients completed the 12-week study phase and three patients discontinued topiramate, two because of side effects and one because of lack of efficacy. There were highly significant improvements between baseline and week 12 on the YMRS and HDRS; the mean YMRS score decreased from 16.3 to 4.3 ( $p=0.0001$ ) (Figure 1), and the mean HDRS score decreased from 14.9 to 6.3 ( $p=0.0001$ ) (Figure 2). Reductions in both YMRS and HDRS scores were significant after 4 weeks of topiramate treatment ( $p=0.0001$ ). Highly significant improvements were also observed in overall CGI-BP-M scores ( $p=0.0001$ ) and in CGI-BP-M subscale scores for manic symptoms ( $p=0.002$ ). The improvement in CGI-BP-M subscale scores for depressive symptoms was not statistically significant (Figure 3).

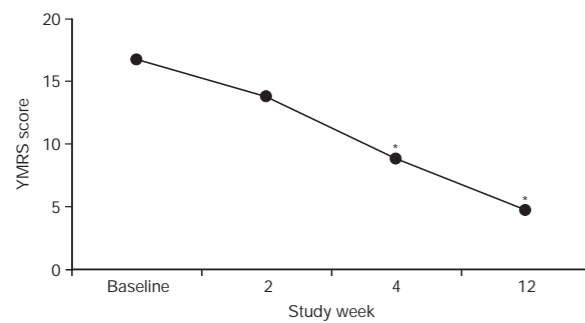


Figure 1  
Change in YMRS scores  
\*p=0.0001 vs baseline

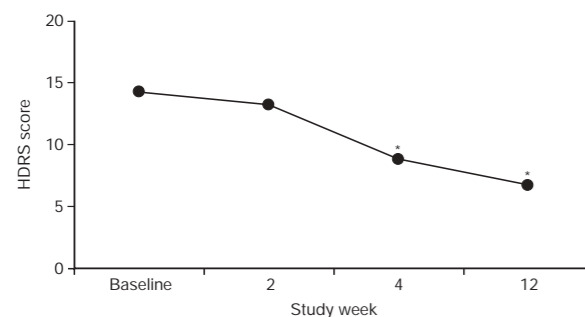


Figure 2  
Change in HDRS scores  
\*p=0.0001 vs baseline

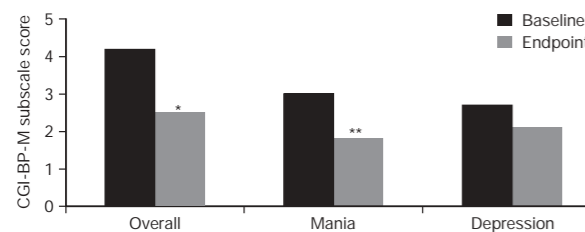


Figure 3  
Change in CGI-BP-M subscale scores  
\*p=0.0001 vs baseline, \*\*p=0.002 vs baseline

Of the 15 patients with hypomania at baseline, eight (53%) were rated as responders to topiramate (50% reduction or more in YMRS scores) and five (33%) were in remission (YMRS score  $\leq 8$ ). In addition, among the four patients with depression at baseline, two (50%) responded to topiramate (50% reduction or more in HDRS scores) and one (25%) met remission criteria (HDRS score  $\leq 6$ ). Rapid

cycling did not seem to have any influence on topiramate response. Four out of seven rapid cyclers were rated as responders. Although no specific rating scales were used, benefits were also observed in some co-morbidities: two bulimic patients and two cocaine abusers reported clinical improvements in binge eating and craving, respectively. One borderline personality disorder patient reported substantial improvement in impulse control. Although placebo response may have to do with these phenomena, other authors have reported improvements in refractory bipolar patients with co-morbid conditions (Guille and Sachs 2002).

Topiramate was generally well tolerated; only two patients discontinued due to side effects (impaired concentration and paraesthesia). Side effects occurred singly or in combination in 12 patients (63%). The most common side effect was impaired concentration (n=4) (Table 3). Six patients (32%) lost weight (mean weight loss  $2.4 \pm 1.9$  kg). No interaction of plasma levels of concomitant mood-stabilisers with topiramate was observed.

Table 3

Incidence of side effects*	n (%)
None	7 (37)
Impaired concentration	4 (21)
Paraesthesia	3 (16)
Nausea	3 (16)
Headache	3 (16)
Dysarthria	1 (5)
Sexual dysfunction	1 (5)
Fatigue	1 (5)
Unpleasant taste	1 (5)
Weight gain	1 (5)
Dizziness	1 (5)
Somnolence	1 (5)

\*Weight loss not included

## Discussion

This open-label study suggests that adjunctive topiramate may be an effective and well-tolerated treatment for bipolar II disorder, improving both hypomanic and depressive symptoms. After 12 weeks of treatment, eight hypomanic patients and two depressed patients had responded to topiramate. Furthermore, five patients with hypomania and one patient with depression were in remission (YMRS score  $\leq 8$  or HDRS score  $\leq 6$ ). Topiramate was well tolerated; the most commonly reported side effects were CNS-related. Two patients discontinued due to side effects (impaired concentration and paraesthesia).

This study should be regarded as preliminary. The open design, absence of a control group, small sample size and concomitant use of other medications are very important limitations. Spontaneous or delayed response to concomitant mood-stabilisers cannot be excluded. However, we think that the 4-week onset of treatment response is less likely to be a result of placebo response, which typically starts at the beginning of the treatment, but rather a result of slow titration of topiramate, which may enhance tolerability, but delay the onset of action of the drug.

Nevertheless, this is the first prospective study to assess the efficacy and safety of topiramate in bipolar II patients.

These preliminary findings compare favourably with data from other open-label studies of topiramate in bipolar disorders (Marcotte 1998; Chengappa et al. 1999; McElroy et al. 2000; McIntyre et al. 2000; Bozikas et al. 2001; Calabrese et al. 2001; Ghaemi et al. 2001; Grunze et al. 2001; Valle-Cabrera et al. 2001; Vieta et al. 2002). In these studies, clinical benefits were reported with topiramate as monotherapy or adjunctive treatment in various presentations of bipolar illness, including acute mania, depression and treatment-refractory rapid cycling bipolar disorder. In this cohort, rapid cyclers seemed to respond as well as non-rapid cyclers. However, topiramate has not proved to be efficacious in the short-term treatment of acute mania in controlled trials (Calabrese 2000) and, therefore, its putative role as a mood-stabilising agent remains unknown. This may have to do with a slow onset of action, not allowing for separation against placebo at week 3, or with a moderate antimanic effect, which may not be enough for fully manic patients but perhaps sufficient for the treatment of hypomania. This phenomenon has been described for other anticonvulsants, such as oxcarbazepine (Hummel et al 2002). The results of our report suggest that the drug should be investigated in the treatment of hypomania and long-term stabilisation of bipolar II disorders. Other drugs, like lamotrigine, have proved to work in bipolar II but not in bipolar I rapid cycling patients (Calabrese et al. 2000).

The mean dose of topiramate at endpoint was 177 mg/day. Experience from open-label studies, mostly in bipolar I disorder, indicates that using topiramate at a dose of 200-400 mg/day with slow titration improves efficacy and tolerability. Hence, it is likely that bipolar II patients may need slightly lower doses.

Weight loss was reported in one-third of the sample, confirming that this side-effect is as common in bipolar disorder patients as in epileptics. Weight loss may be beneficial for

many bipolar patients, who may be overweight, suffer from binge eating problems, or take medications that induce weight gain.

## Conclusion

In conclusion, our findings suggest that topiramate may be useful as adjunctive treatment for bipolar II disorder. Controlled trials are now needed to confirm the mood-stabilising effects of topiramate and its potentially beneficial effects on weight gain and other related co-morbidities.

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## Creatine Kinase BB in Brain in Schizophrenia

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### Summary

*Creatine kinase (CK) is responsible for the creatine/ creatine phosphate level, which is known to alter in the brain of patients with schizophrenia. A comparative estimation of CK enzymatic activity and immunoreactivity of CK BB was carried out in readily soluble extracts from frontal cortex, anterior and posterior cingulate cortex, hippocampus and cerebellum from brains of individuals with schizophrenia versus normal controls. CK activity was determined using a commercial diagnostic kit. CK BB immunoreactivity was evaluated by ECL-immunoblotting using monoclonal antibody. A drastic drop of CK activity and CK BB immunoreactivity was observed in all the examined brain areas in schizophrenic patients compared to controls (p<0.01), with the maximum drop in the cerebellum. The reduction was independent of age, postmortem interval or chlorpromazine equivalent. The decreased level of CK BB in schizophrenia was confirmed by purification of CK BB from brains of patients with schizophrenia and control brains: the yield of the purified enzyme was significantly lower in schizophrenia, wherein molecular masses of CK B-subunits were equal. Possible causes and consequences of the decrease in CK BB level observed in brain of patients with schizophrenia are discussed.*

**Key words:** creatine kinase BB, ECL-immunoblotting, human brain, schizophrenia.

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### Introduction

Several lines of evidence suggest changed levels of high-energy phosphates in the cortex of schizophrenic patients. Recently a noninvasive technique, <sup>31</sup>P magnetic resonance spectroscopy (MRS), has enabled changed levels of ATP and creatine phosphate (CrP) in the frontal lobe of schizophrenic patients to be revealed (Volz et al. 1997, 1998, 2000a,b; Deicken et al. 1994; Williamson et al. 1991; Fukuzako 2001).

Besides changed concentrations of ATP and CrP, alterations in creatine (Cr) levels for schizophrenic patients compared to controls have been reported (Tunstall et al. 2000; Fukuzako 2001).

Creatine kinase (CK) catalyzes reversible CrP conversion into Cr. Being the key enzyme of the Cr/CrP system, cerebral CK is present in two isoforms, cytosolic readily solubilized CK BB and mitochondrial CK isoform (Mi-CK). Cytosolic CK BB can both utilize CrP to convert ADP to ATP at sites of energy demand and convert ATP to CrP for energy storage, whereas Mi-CK preferentially utilizes the ATP synthesized from oxidative phosphorylation to convert Cr to CrP for export to the cytoplasm (Wallimann et al. 1994, 1992).

The altered level of the main substrates and products of CK reaction in brain in schizophrenia may indicate alteration of quantity or changed functioning of the enzyme molecules. Moreover, according to the opinion of some investigators, CK may be considered as a marker of Cr/CrP system functioning in brain (Tsuji et al. 1994). At present, information on impaired functioning of CK in schizophrenia is not yet accumulated.

In our early work the decrease in CK enzymatic activity was found in frontal cortex extracts from brain of patients with schizophrenia (Burbaeva et al. 1987). Later, a significant decrease was revealed in CK BB level in brain (frontal cortex and hippocampus) of patients with schizophrenia versus controls using the analysis of water-soluble brain extracts by two-dimensional PAGE (Smirnov et al. 1991; Klushnik et al. 1991a) or by the native gel electrophoresis technique (Klushnik et al. 1991b).

Immunochemical evaluation of CK BB immunoreactivity in frontal cortex and

hippocampus provided evidence of a decreased CK BB immunoreactivity level in patients with schizophrenia (the study was accomplished using polyclonal antibodies against human CK BB in Western blotting) (Burbaeva et al. 1990 a, b, 1996).

In contrast to our previous studies, in the present work we used monoclonal antibody in evaluation of CK BB immunoreactivity in extracts of postmortem brain. This monoclonal antibody against human CK BB is directed specifically to this isoform (no cross-reactivity with Mi-CK). Also, immunoblotting with enzyme-chemiluminescent amplification of the signal (ECL-immunoblotting) was employed, which enables quantification (semi-quantitative evaluation) of the data in a comparative study. To compare with previous investigations, the spectrum of brain areas under study was broadened and embraced frontal cortex (Brodmann area 10), anterior and posterior cingulate cortex (areas 24 and 23), hippocampus and cerebellar cortex. All these areas were included in the present study due to substantial metabolic (including energy metabolism) impairments found in these areas in schizophrenia (Deakin et al. 1997; Katsetos et al. 1997; Tamminga et al. 2000; Grace 2000; Fukuzako 2001).

## Methods

Brain tissues were obtained at autopsy of chronically hospitalized patients with schizophrenia diagnosed premortem according to ICD-10 criteria in the Clinical Department of the Mental Health Research Center of the Russian Academy of Medical Sciences (MHRC RAMS), Moscow. Brain tissues obtained at autopsy of persons with no history of mental and neurological disorders and drug treatment served as controls. The samples of frontal cortex (Brodmann area 10), anterior and posterior cingulate cortex (areas 24 and 23), hippocampus and cerebellar cortex of postmortem brain (left hemisphere) from controls and patients with schizophrenia were dissected and processed at 4°C, frozen in liquid nitrogen and stored at -80° until use. Not all brain regions were available for all subjects. Brain samples from both groups of subjects were stored for a comparable length of time before use. Information regarding final diagnoses, post mortem intervals, illness duration, family forms, medication and gender for the patient group is summarized in Table 1. There were no significant differences for age (mean age was 60.0 ± 14.5 years for patients and 55.7 ± 14.0 years for controls) and postmortem interval (PMI) (mean PMI was 7.2 ± 3.8 h for patients and 7.0 ± 1.8 h for controls) between schizophrenic and control subjects. In both groups, the cause of death was generally cardiac failure and terminal respiratory condition.

Table 1  
Subject characteristics

Gender	Age (y)	Diagnosis	Duration of illness (y)	Family Form	Chlorpromazine Equivalent doses (mg)	PMI*** (h)
f	69	F20.00	15	N*	1	6
m	80	F20.02	26	N	51	6.5
f	36	F20.00	26	F**	60	4
m	66	F20.50	47	F	4	6
f	67	F20.00	11	N	16	14
f	75	F20.00	23	N	17	4.5
f	67	F20.02	5	F	101	5
f	39	F20.02	9	F	0	5
f	54	F20.31	10	N	25	6
m	69	F20.00	21	N	108	6
f	65	F20.00	22	N	105	8
f		F20.X2 (F20.22)	27	N	78	18
f	56	F20.02	22	N	10	4
f	77	F20.02	20	N	333	5.5
f	49	F20.02	25	F	128	8.5
m	41	F20.31	10	N	29	4.5
f	68	F20.02	14	N	21	12

N\* - non familial form; F\*\* - familial form; PMI\*\*\* - postmortem interval

The study was performed in accordance with an approved protocol of the Ethics Committee of the MHRC of RAMS. The chlorpromazine equivalent was estimated according to Davis (1974).

Preparation of brain samples for the study of enzymatic activity and immunoreactivity included homogenization of 200 mg of tissue in 1 ml of 20 mM Tris-HCl buffer, pH 7.0, containing 1.4 mM 2-mercapto ethanol using glass-teflon homogenizer at 0-4°C, with subsequent centrifugation at 1000 g for 15 minutes, followed by centrifugation at 100 000 g for 1 hour at 4°C. The final supernatant was used for CK activity and CK BB immunoreactivity determination. CK enzymatic activity was determined in accordance with the protocol of Sigma Co, St. Louis, using the standard diagnostic kit (Cat. No 661-PB). The specific activity of CK is given in Sigma units/ml per 1 mg of protein. Protein concentration was determined according to the method of Lowry et al. (1951). Monoclonal antibodies (MAb) were produced according to the method described by Nikulina et al. (2000). MAb were purified by ion exchange chromatography and conjugated with horseradish peroxidase. Specificity of MAb obtained was verified by ECL-immunoblotting using CK BB, CK MM, and Mi-CK isoforms purified according to corresponding protocols (Keutel et al. 1972; Wyss et al. 1990). Of 15 clones tested, only 19E10 possessed no cross-reactivity with Mi-CK or CK MM in ECL-immunoblotting. Samples of brain protein extracts were assayed for total protein content, aliquots were matched by protein content (30 µg of protein), denatured and separated by SDS-PAGE in 10% polyacrylamide slab gels (Laemmli 1970). The proteins were electrotransferred on to nitrocellulose membranes for ECL-immunoblotting according to Towbin (1979) using anti-CK BB monoclonal antibodies conjugated with horseradish peroxidase, with subsequent chemiluminescent amplification of signal according to the protocol for ECL-immunoblotting (Amersham - Pharmacia Biotech). The "arbitrary units" used for comparison of CK B immunoreactivity are derived and calculated from the results of controls. Quantitative analysis of electrophoregrams after ECL-immunoblotting was performed using a Zeineh laser densitometer and corresponding software (Biomed Instruments, USA). Statistical analysis was performed using Excel (Microsoft) and STATISTICA (for Windows, StatSoft, Inc., USA, non-parametric analysis) software. Data in the demographic table are expressed as means ± standard deviation (SD). Results are expressed in units of CK enzymatic activity or arbitrary units of immunoreactivity. Each point on the figures is a mean calculated from three measurements for each patient; the median for each group of cases is given. The significance of the differences between groups was calculated using the non-parametric Mann-Whitney U-test.

## Results

### • Comparative CK activity determination in brain extracts

CK activities measured in protein extracts from brains of controls and patients with schizophrenia are presented in Figure 1. For controls (in spite of data scatter for each individual) the distinct distribution pattern of CK activity level among the five brain areas was typical: the highest level in cerebellum ( $p < 0.01$  in comparison to the others), the lowest in hippocampus ( $p < 0.01$  in comparison to the others), no significant difference was observed between frontal cortex, anterior and posterior cingulate cortex (medians are given in Table 2). The extremely high CK activity found in cerebella of controls is in agreement with the observations on animal (Manos et al. 1991; Wallimann and Hemmer 1994; Binderman et al. 1988) and human brains (Kanemitsu 1988).

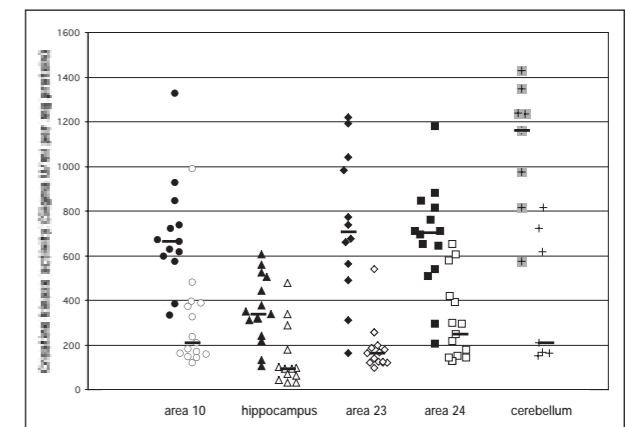


Figure 1  
Specific activity of creatine kinase (Sigma Units/ml per 1 mg of protein) in extracts from brain areas of controls (solid markers, left in each pair for distinct brain area) and patients with schizophrenia (open markers, right in each pair for distinct brain area). Medians are given for each group as dashes; differences between medians are significant ( $p < 0.01$ ) for all brain areas.

Table 2

Differences in creatine kinase activity (median) between the control and schizophrenia groups

Cortex	Control Median (CM)	Schizophrenia Median (SM)	CM/SM Ratio
Frontal	665	210	3.1
Anterior cingulate cortex	702	247	2.8
Posterior cingulate cortex	707	163	4.3
Hippocampus	337	95	3.5
Cerebellum	1163	208	5.5

For patients a substantial and significant decrease of CK enzymatic activity was revealed in extracts from samples of all studied cortex area (frontal cortex, anterior and posterior cingulate cortex, hippocampus, and cerebellum cortex) compared to controls ( $p < 0.01$ ) (Figure 1 and Table 2).

As seen from Figure 1, the extent of the CK activity decrease varied in various brain areas. In fact, the most prominent difference (about 5.5 times) between medians calculated for two groups was observed in cerebellum, whereas the decrease in posterior cingulate cortex (4.3 times), hippocampus (3.5 times), frontal cortex (3.1 times), and in anterior cingulate cortex (2.8 times) was also significant ( $p < 0.01$ ) (Table 2). Thus, distribution of CK activity level among brain areas was changed compared to controls: even distribution with no significant difference between areas in CK activity levels was observed in the patient group.

The reduction of CK activity may be attributed to the decrease of the CK BB content in readily solubilized brain tissue fraction. To test this assumption, the evaluation of CK B-isoform immunoreactivity levels in brain tissue extracts, as well as direct purification of the enzyme from brain tissue was performed.

#### • Comparative CK BB immunoreactivity determination in brain extracts

To detect the presence of different CK isoforms in brain (CK BB and Mi-CK consisting of subunits of equal molecular masses with homologous amino acid sequences and close related one requires the use of specific monoclonal antibodies to avoid interference from the cross-reactivity between different isoforms in immunochemical (Western blot) analysis. Hence, the monoclonal antibody mono-specific to CK B-isoform was used for evaluation of CK-B immunoreactivity.

CK B-subunit immunoreactivity values were evaluated in the same fractions of brain samples, as in the case with CK activity. The CK B-subunit immunoreactivity levels in all analyzed brain areas of patients with schizophrenia were significantly decreased compared to controls ( $p < 0.01$ ) (Figure 2).

The extent of the CK B-subunit immunoreactivity decrease varied among brain areas: it was more prominent in area 23, 24, hippocampus and cerebellum than in area 10 (the frequencies of negative staining in these areas are obviously higher than in area 10 (Figure 2)). Among the structures under study the maximal median decrease was observed in cerebellum, as in the case of CK enzymatic activity.

The reduction of CK activity or CK B-subunit

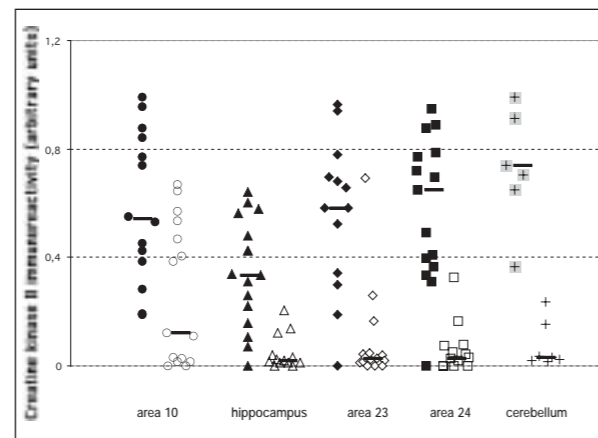


Figure 2 Immunoreactivity of creatine kinase B-subunit (in arbitrary units) in extracts from brain areas of controls (solid markers, left in each pair for distinct brain area) and patients with schizophrenia (open markers, right in each pair for distinct brain area). Extracts (30  $\mu$ g of total protein/lane) from indicated brain areas were separated by SDS-PAGE and subjected to ECL-immunoblotting (staining with monoclonal anti-CK BB antibodies), then corresponding spot densities on films were quantified by scanning densitometry. Medians are given for each the group as dashes; differences between medians are significant ( $p < 0.01$ ) for all brain areas.

immunoreactivity did not depend on age, postmortem delay or chlorpromazine equivalent.

#### • Purification of CK BB from brain tissue

The decrease of CK B-subunit immunoreactivity observed in schizophrenia may be due to the decrease of CK BB protein content in readily solubilized brain tissue fraction. To verify the supposition, CK BB purification from control brains and brain of patients with schizophrenia was performed.

CK BB was purified from readily solubilized protein fraction of brain tissue in accordance with Keutel et al. (1972).

Molecular masses of CK B-subunits purified from control brain and from brains of patients with schizophrenia were indistinguishable on PAGE (data not shown), whereas the CK BB protein yield from brains with the pathology (three cases) was ~8 times lower, than from controls (three cases) and comprised  $1.0 \pm 0.2$  mg in schizophrenia versus  $9.0 \pm 0.1$  mg from 100 g of brain tissue in control.

#### Discussion

The reviewed data on deviations in ATP and/or CrP levels give evidence for substantial abnormalities in energy metabolism in brain of patients with schizophrenia (Fukuzako 2001).

Since CK regulates ATP/PCr levels, the altered contents of the main substrates and products of CK reaction in brain of patients with schizophrenia may indicate an impairment of the

enzyme. In fact, in the present work a drastic drop of CK activity and CK B-subunit immunoreactivity was found in readily solubilized extracts of postmortem brain from patients with schizophrenia. Moreover, decreased yield of CK BB was obtained as a result of the enzyme purification from brain tissue of patients with schizophrenia compared to controls, suggesting decreased content of CK BB cytoplasm of brain cells in patients with schizophrenia.

Several reasons for this phenomenon may be supposed. Postmortem interval was found to have negligible influence on CK activity in the first 18-20 hours after death. Nevertheless, to exclude any possible artifacts due to autolysis, patient and control groups were matched by postmortem interval.

Neuroleptic effect is the second most important factor to be taken into consideration (Volz et al. 1998). PCr and ATP levels were found to be increased in the frontal lobe of neuroleptic-treated patients with schizophrenia compared to control subjects (Volz et al. 1997) and the authors hypothesized that neuroleptics might lead to a decrease in the energy demand process. In the present work no correlation was found between chlorpromazine equivalent and CK activity or CK BB immunoreactivity in brains of patients with schizophrenia. No influence of chlorpromazine or haloperidol intramuscular injection on CK activity or CK BB immunoreactivity in rat brain was observed earlier (own unpublished data). Moreover, our study on a group of neuroleptic-naive patients with Alzheimer's disease also provided evidence for CK activity and CK BB immunoreactivity decrease in the brains of patients compared to controls (Burbaeva et al. 1990a,b, 1992). Hence, the CK BB decrease observed in brain of patients with these diseases seems to be a characteristic feature of these disorders and does not result from therapy with neuroleptics.

Alteration of the respective gene expression may be supposed as a reason for changes in CK activity and CK BB immunoreactivity. Previously, an attempt was made to determine the level of mRNA for CK B subunit in postmortem brain, wherein the level of CK mRNA was found to be unchanged in brain from patients with schizophrenia compared to controls (Spunde 1993). The same fact was reported for brain from patients with Alzheimer's disease: a drastic decrease of CK BB level was accompanied by unchanged mRNA level for CK B-subunit (Aksenov et al. 2000).

Another cause of CK BB level decrease observed in readily solubilized extracts from brain of patients with schizophrenia might be re-distribution of the enzyme among sub-cellular fractions. In fact, alteration of CK BB sub-

cellular localization was observed in schizophrenia (Kluschnik et al. 1991b) and Alzheimer's disease (David et al. 1998). For both pathologies, the decrease of CK B-isoform level in cytoplasm was accompanied by increase of this isoform in the membrane fraction. Based on this observation, a translocation of readily solubilized CK BB form into the compartmentalized one was proposed.

Hence, evidence that cerebrospinal fluid concentrations of CK are unchanged (Zweig et al. 1981) or even elevated in psychosis (Vale et al. 1974) seems not to conflict with our findings of decreased CK-BB content in the brain of patients with schizophrenia.

Since the extent of enzyme extraction obviously depends on its cellular localization and the extraction method, it is easily explained why some authors did not find any alterations in CK BB protein level in mental pathologies (Johnston-Wilson et al. 2000). These authors employed an extraction method which differs substantially from ours.

Elevated hydrophobicity of the CK BB molecule as a cause of its re-distribution between readily soluble and membrane fractions ("translocation") in Alzheimer's disease was described by David et al. (1998) and similar processes may take place in schizophrenia. The alteration of hydrophobicity may be due to some modification of the enzyme molecule influencing its activity and immunoreactivity. In particular, oxidative damage may be one of such modifications.

A post-translation oxidative modification was supposed to be a possible cause of the observed decrease of CK activity and CK BB immunoreactivity (Aksenov et al. 2000). In fact, a CK BB active site is susceptible to oxidative modification (Forstner et al. 1997), and the decreased CK activity in brain was supposed to reflect the elevated oxidative damage of proteins, particularly in Alzheimer's disease (Aksenova et al. 1999, 2000). In schizophrenia, the decrease of CK level may also result from oxidative modification. However, alterations of activity and immunoreactivity of glutamine synthetase, another representative enzyme which is believed to be susceptible to oxidative modification, are not so drastic compared to CK BB in brain of patients with schizophrenia (Tereshkina et al. 2000). Thus, oxidative damage seems to be not the sole reason for CK BB level decrease found in schizophrenia.

Phosphorylation is known to be a regulating factor for CK activity (Quest et al. 1990; Ponticos et al. 1998). Hence, phosphorylation may also result in CK activity decrease in mental pathology. The hypothesis on CK BB abnormal

phosphorylation in schizophrenia is attractive, since several protein kinases, such as MAP kinases and casein kinase 2, are changed in the brains of patients with schizophrenia, and drastic alterations in protein phosphorylation in schizophrenic brain were discovered (Kynosseva et al. 1999; Aksenova et al. 1991).

To conclude, whatever the cause of CK BB alteration in the brains of patients with schizophrenia, without a doubt this decrease leads to drastic disturbances in brain energy metabolism, and all these events may be involved in the pathogenesis.

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## A Stubborn Behaviour: the Failure of Antidepressants to Reduce Suicide Rates

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### Summary

Over the past decades the rate of completed suicide has remained quite stable, that of suicide attempts even seems to have increased (to the extent it has been studied in defined regions). These are puzzling observations, since depression is the major suicide precursor and since antidepressants over the years have been increasingly used in the treatment of depression. These observations have not attracted sufficient attention, possibly because they do not accord with consensus opinions about depression treatment in psychiatry today. In this paper a number of possible explanations are discussed. They not only deserve but are definitely in need of systematic investigation.

**Key words:** depression, suicide rate, antidepressants, psychotherapy, suicide research.

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### Introduction

- Have antidepressants reduced suicide rates? Negative results.

Depression is considered to be a major suicide precursor. Psychological autopsy studies show that approximately 90% of consecutive suicide victims qualified for an axis I diagnosis at the time of suicide: 60 to 90% suffered from a subtype of depression; 8-10% from schizophrenia or a substance-related disorder (Wasserman 2000). An estimated 50% of those who die through suicide have suffered from depression (Isometsä et al. 1998). The percentage of patients that will die by suicide is estimated to be 15-19% in those ever hospitalised for depression (Guze and Robbins 1970; Goodwin and Jamison 1990). Lower figures are reported for depressed out-patient populations (Bostwick and Pankratz 2000). The rate of attempted suicide in depression, though not exactly known, is much higher.

A major strategy in the treatment of depression, both major depression and dysthymia, is prescription of antidepressant drugs. The use of those drugs has risen substantially over the years. In The Netherlands, for instance, the increase came to 12% yearly over the past four years. Of course antidepressants are also used in other conditions, but depression still remains the main reason for their prescription.

Rightly, then, one may expect suicide rates to have gone down, in proportion. This, however, did not happen. Suicide rates differ considerably from country to country and from region to region (Diekstra 1995). Allowing for that, in most countries the rates of completed suicide seem to be quite stable (Table 1). In The Netherlands, for instance, the number has been approximately 1500 per year, for many years now. Worldwide, for men the trend is slightly upward, for women the curve runs horizontally (Figure 1). In some countries the rise in suicide is particularly pronounced in males between 15 and 24 years of age (Lester and Yang 1998). Overall rates of suicide attempts are not known, but in certain delineated areas they have tended to rise rather than to decrease (Hawton et al. 1997).

Table 1

Suicide per 100,000 inhabitants in selected countries

	1980-1984	1985-1989	1995
France	20.6	20.8	20.4
Spain	5.5	7.1	8.1
Italy	7.3	7.3	7.9
Germany	20.8	16.5	15.8
Poland	13.0	13.4	14.3
Portugal	8.7	8.7	8.2
England + Wales	8.7	7.9	6.9
Australia	11.6	12.8	1.8
USA	12.2	12.4	12.0

Source: World Health Statistics Annual; 1996

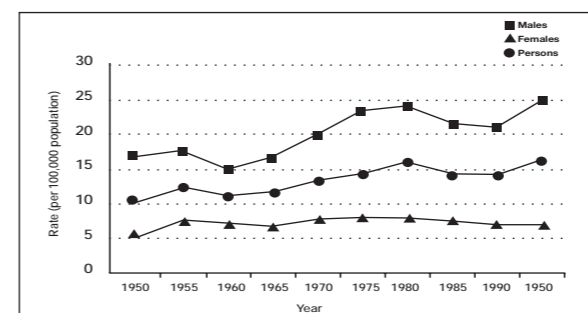


Figure 1  
World Health Organisation (1999) Figures and facts about Suicide. World Health Organisation, Geneva.

Surely the latter observation should not be generalized. An international study, comparing rates of suicide attempt in 16 different European regions, showed that those figures varied from year to year and from region to region (Kerkhof 2000). In some regions the frequency increased slightly between 1989 and 1992, in others a likewise small reduction was observed. A robust and overall decline in the rate of attempted suicide, however, could not be demonstrated.

Furthermore, and rather alarmingly, Khan et al. (2000) reported that rates of suicide and attempted suicide did not significantly differ in depressed patients treated with either placebo or an antidepressant. They analysed short-term studies with seven new antidepressant drugs, (fluoxetine, sertraline, paroxetine, venlafaxine, nefazadone, mirtazapine and bupropion) using the USA Food and Drug Administration database. The study encompassed 19,639 patients. Annual rates of suicide and attempted suicide were 0.4% and 2.7% with placebo, 0.7% and 3.4% with active competitors (imipramine, amitriptyline and trazadone) and 0.8% and 2.8% with the investigational drugs. Analysing studies carried out with venlafaxine ER and citalopram, in which 23,201 patients had participated, produced comparable data (Khan et al. 2001).

In analyses of 77 studies with antidepressants, carried out in The Netherlands between 1983 and 1997 encompassing 12,246 depressed

patients, similar conclusions were reached: suicide attempt rates did not differ significantly between placebo and experimental groups. These studies were part of a registration dossier of the Medicines Evaluation Board, being the regulatory authority of The Netherlands (Storosum et al. 2001).

- Have antidepressants reduced suicide rates? Positive results.

Long-term, controlled, prospective studies into the impact of antidepressants on suicide risk are scarce, but some have reported positive effects (Beasley et al. 1991; Roy 2001). Some data suggest that selective serotonin reuptake inhibitors (SSRIs) are superior in this respect to 'broad spectrum antidepressants' (Montgomery et al. 1995; Kasper et al. 1996). However, this difference disappeared after six weeks of treatment (Mann and Kapur 1991). Others, however, failed to find a specific anti-suicidal effect of SSRIs (Malone and Moran 2001).

The relevant studies, however, are unconvincing. They do not allow conclusions to be drawn about possible beneficial effects of antidepressants on suicide rates, and this for several reasons. They generally concern short-term studies with a limited number of patients. To demonstrate statistically that antidepressants produce an antisuicidal effect one needs, Isacson et al. (1996) calculated, at least 20,000 depressed patients randomly treated with either antidepressants or placebo. The studies reporting positive effects, however, were relatively small and not placebo-controlled. They are, moreover, not controlled for help-seeking behaviour nor for concomitant psychotherapeutic treatment. Hence it is conceivable that the positive results in the antidepressant groups, relative to the untreated groups, are due to a greater propensity to seek professional help in times of mounting stress or of psychotherapeutic intervention.

Finally, one has to keep in mind that serious suicidality is usually an exclusion criterion in placebo-controlled, therapeutic studies with antidepressants. This makes it hard to draw conclusions on the impact they exert on suicidality.

Based on the data derived from a pharmaco-epidemiological study including Sweden's entire population, Isacson et al. (1996) concluded that the application of antidepressants had reduced the risk of completed suicide 1.8 times, relative to depressed patients not using antidepressants. The study, however, comprised no placebo-treated group. It is unclear, moreover, whether and if so what kind of non-pharmacological, particularly psychological, interventions had been practised and whether both groups differed in that respect. Hence the

conclusions drawn by Isacson et al. (1997) seem to me premature. They themselves consider that conclusion to be strengthened by the observation that, parallel to the increase in prescription rate of antidepressants since the 1970s, the suicide rate has declined. However, in the past decades, both doctors and patients became increasingly aware of what depression is and how to treat it. This has led to earlier diagnosis and more intensive treatment. In this period, moreover, new and effective psychological intervention techniques have been developed. They are employed with or without antidepressants. Therefore, it is not justified to pass the observed reduction of suicide rates simply to the credit account of antidepressants.

The well-known Gotland study showed that, after intensive postgraduate training of general practitioners on recognition and treatment of depression, suicide mortality showed a marked reduction (Rutz et al. 1989; Pihlgren 1995). In the same period the prescription of antidepressants increased. The two phenomena were assumed to be causally related. This conclusion, however, is premature. Since one may presume that, due to professional instruction, the doctor/patient relationship was strengthened and more attention was paid to attitude, to development of a supportive connecting demeanour, and since these effects were not accounted for, these results, too, are not conclusive.

The data regarding lithium are more encouraging. Administered as a mood stabiliser in bipolar and recurrent unipolar depression, it was found to reduce suicide risk substantially, relative to depressed patients not treated with lithium (Tondo et al. 1997). This has not been demonstrated with other mood stabilisers. Some data suggest that lithium can exert antisuicidal effects even if it fails to effect mood-stabilisation (Müller-Oerlinghausen et al. 1992). The hypothesis that suicidality can be pharmacologically influenced independent of mood regulation/normalisation is scientifically and clinically interesting and certainly deserves further study.

One has to keep in mind, however, that lithium clinics/programmes generally do not rest on lithium alone, but offer in addition psycho-educational and other group-orientated programmes. Most of the long-term lithium studies do not control for that. Definitive conclusions about the antisuicidal potency of lithium have to await prospective, double-blind, placebo-controlled studies in which the groups are treated in similar fashion, pharmacologically and psychologically.

Patients with personality disorders, in particular those categorized as borderline patients, constitute another patient group with an increased suicide risk, for whom antidepressants are a therapeutic option. Few placebo-controlled

studies have been published on the effect of antidepressants on suicidality and aggression regulation in this group of patients. They concern particularly the SSRIs. According to Coccaro and Kavousi (1997) outward directed aggression responds favourably. Verkes et al. (1998) studied the effect of paroxetine versus placebo in 91 suicidal, non-depressed patients with personality disorders, mainly of the borderline type. The study extended over a period of one year. In the group as a whole paroxetine had no effect on the rate of suicide attempts. In the subgroup of patients who had attempted suicide five times or more in the previous years, paroxetine did reduce the number of suicide attempts significantly. These data await confirmation and further exploration.

Taking all these data together, I arrive at the conclusion that one can advance only few and rather weak arguments against the thesis that suicide remained stubbornly present in the era of antidepressants. Rihmer (2001) disagrees. He stated that the antidepressant era has shown a reduction in suicide rate: "The sometimes presented statement ("increasing use of antidepressants did not reduce suicide rates") is counterproductive, rather than a counter-argument." By and large, the available facts, however, do not support this notion. Facts are just facts. They refuse to be qualified as productive or counterproductive. These can be qualified as such. Facts can support or repudiate a thesis. If the thesis represents a desirable condition but the facts are non-supportive, the appropriate thing to do is to analyse the data as to their origin and do one's utmost to generate facts that *are* supportive.

In the following, I carry out the first exercise. What might be the reasons that the suicide problem proved so obstinate? Some possible explanations are discussed.

- Coincidence

Depression and suicidality are unrelated states. Their co-occurrence is a matter of coincidence and hence it is not to be expected that suicide rates will be affected by treatment of depression. This is not a likely explanation. First, because in that case one would expect suicidality to occur as frequently in the depressed as in the remitted state, and this is not the case. Suicide risk is to a high degree state-dependent and by far at its greatest during a depressive episode (Roy 2001). Psychopharmacological data, moreover, render it unlikely that depression and suicidality are disconnected. Montgomery et al. (1994), for instance, found that the SSRI fluoxetine is ineffective in brief recurrent depression, both with regard to depression and to suicidality.

Second, experiential data are contradictory. Depressed patients themselves generally experience a strong connection between

feelings of hopelessness and suicidal tendencies. Experiential data have substantial evidential power in psychiatry. The observation that suicide risk correlates more strongly with feelings of hopelessness, as measured with the Beck scale, than with depression as such is a case in point. Hopelessness, moreover, may occur independent of depression or to a degree discrepant with depression severity (Mann et al. 1999).

Experiential, that is subjective, data are not held in high esteem in today's research circles, preoccupied as they are with assessment of data that can be established with a fair degree of objectivity. Subjective data are conceived as "soft", because they are alleged to be not measurable and reproducibly. This view is prejudiced (Van Praag 1992). Methods are available to measure and to follow up, prospectively and in a systematic and careful way, individual mood states and related cognitions. I am alluding to the experience sampling method. Though, regrettably, so far only sparingly used, the results obtained underscore the diagnostic importance of subjective psychopathology (Van Eck et al. 1998; Myin-Germeys et al. 2001). There is no convincing justification for neglecting substantial domains of psychopathology because they are subjective (van Praag 1992, 1997).

- Continuity of treatment

Continuity of treatment is not well looked after in patients with recurrent unipolar depression, even if their history records suicide attempts (Isacson et al. 1997; Druss et al. 2000; Lecrubier 1998; Oquendo et al. 2002). Only 17% of a group of patients with major depression were prescribed antidepressant medication one month after a suicide attempt (Suominen et al. 1998). For many patients with recurrent depression it appears to be difficult, moreover, to take medicines faithfully over long periods of time.

It is thus conceivable that the small effect antidepressants have had on suicide rates is due to discontinuity of treatment, resulting from misconceptions by the doctor or a lack of perseverance on the part of the patient. This explanation shifts responsibility from the remedy to the consumer and/or prescriber. If correct, 'continuing education' of both parties should receive top priority.

It is, however, improbable that this conjecture holds good for the data of Khan et al. (2001) and Storosum et al. (2001) referred to above. They are derived from controlled trials and in those studies strict control of medication intake, generally, gets full attention.

- Efficacy of antidepressants

Antidepressants may be less effective than is generally accepted. If so, one cannot expect antidepressant treatment to have a major

impact on suicidality, being frequently a complication of the depressed state. This is not an unreal proposition. The response to antidepressants is quite often partial: residual symptoms then persist (see "Residual symptoms" below). Moreover, re-emergence or worsening of depressive symptoms during maintenance treatment with antidepressants is a common occurrence. It was found to occur in 9-57% of patients in published studies (Byrne and Rothschild 1998). Many studies over the past 20 years showed generally modest effect when comparing placebo and antidepressant drugs. A case in point is the study of Khan et al. (2000) cited above, reporting symptom reduction of 40.7% with investigational drugs, 41.7% with active comparators and 30.9% with placebo. In a meta-analysis of 33 antidepressant trials Bollini et al. (1999) found an average improvement of 53% versus 35% for placebo. The initial findings with antidepressants in the 1960s and 1970s were much more encouraging, reporting at least 30-35% placebo/drug differences (Van Praag 1978). If one is not satisfied with the easiest (but unsatisfactory) way out of declaring those data antiquated and invalid then, once more, the question can be posed: how come? I will discuss a few possible explanations.

*Blurring of syndromes and neglect of psychogenesis*

Before the introduction of DSM III diagnosis in psychiatry was, it is true, not standardised, but it was detailed, at least in Western Europe. Two philosophies were dominant at the time: phenomenology and psychoanalysis. The first required precise accounting of symptomatological and experiential data; the second a detailed analysis of developmental factors possibly or supposedly involved in the aetiology of the disorder.

With the introduction of DSM III, syndromal differentiation became a thing of the past. Symptomatologically, one qualifies for a particular diagnosis if x out of a series of y symptoms are demonstrable, irrespective which ones. One diagnostic category, for instance major depression or dysthymia, therefore covers a variety of syndromes. This approach has severely compromised diagnostic acuity. It is presently impossible to establish whether a particular antidepressant is preferentially effective in a particular depressive syndrome. There are, however, strong indications that those preferences do exist. Tricyclic antidepressants, for instance, were shown to be more helpful in endogenous than in non-endogenous depression (van Praag 1962; Heiligenstein et al. 1994; Roth 2001).

If, in the study of antidepressants, presumably responsive and less- or non-responsive patients are lumped together, the effectiveness of the drug will drop and approach the placebo response.

In the DSM classification, furthermore, the concept of psychogenesis all but disappeared. Axis I and Axis II disorders are registered independently. An assessment – hypothesis, if one so wishes – of the relation between developmental adversity and personality deviations on the one hand, and Axis I diagnosis on the other is no requirement. A quintessential issue in psychiatric diagnosis is disregarded. With that, the role of psychotherapy in the treatment of depression declined, which might have diminished the therapeutic yield of antidepressant drugs (see “Stepchild psychotherapy” below).

The DSM system brought standardization of psychiatric diagnosis, but at the same time, considerable impoverishment (Van Praag et al. 1987; Van Praag 1992).

#### *Border problems*

In recent years more and more subjects with depressive symptoms have been marked as candidates for treatment with antidepressants. The border between distress and depression, between worrying and a true mood disorder is, however, ill-defined (Van Praag 2000). Distressed people and worriers cannot be expected to respond to antidepressant drugs. If an experimental group is made up of depressed and distressed individuals the response rate obtained with an antidepressant will be low and presumably lower than if only people with ‘case-depression’ had participated. As an analogy: if one aspires to explore the efficacy of antibiotics in pneumonia one should guard against inclusion of patients with a common cold in the experimental group. This would result in underestimation of their therapeutic potential.

#### *Stepchild psychotherapy*

The excessive confidence in the therapeutic power of psychological methods in treating depression, prevailing in the 1960s and 1970s, has been offset by a heavy reliance on antidepressant drugs as monotherapy, that is not in conjunction with psychotherapy. This might explain disappointing results obtained with antidepressants alone. Mood disorders frequently occur in subjects with personality disorders or deviant personality traits (Van Praag et al. In Press). Personality frailties may play an important role in the aetiology of mood disorders. Personality imperfections do not generally respond to antidepressants, but require psychological interventions. It is known, moreover, that personality disorders diminish the efficacy of antidepressants in depression (O’Leary and Costello 2001). Exclusive reliance on antidepressants alone, at the expense of additional psychological interventions aimed at ego-strengthening and defence-intensification, will inevitably reduce the therapeutic return.

#### *Worrying rather than depression is the main precursor of suicide*

Many people worry; only a minority of those suffer from depression. Depressed worriers have a fair chance to improve on antidepressants, worriers without depression probably not. I use the term ‘probably’, because it is unknown what the response to antidepressants is in this group. If worriers, like depressives, are at increased risk for suicide one cannot expect antidepressants to reduce significantly overall suicide rates.

The matter is unknown. As stated in the section “Border problems” above, the border between worrying and depression is undetermined. We do not even know what the relevant criteria are: number of symptoms, kind of symptoms, their severity or duration, social and professional incapacity, degree of subjective suffering. As long as this border is undetermined the suicide risk among worriers cannot be determined.

- Residual symptoms

In a substantial proportion of depressed patients treatment with antidepressants does not result in full recovery; residual symptoms persist (Fava 1999; Agosti et al. 1993; Faravelli et al. 1986; Sonino and Fava 2002). Those can be true remnants of the depressive syndrome or manifestations of disappointment that treatment has been less successful than was hoped for. In this way suicidal tendencies might be maintained or triggered.

- Personality traits

Depression and personality deviations often occur together (Hirschfeld et al. 1983; Clayton et al. 1994). Stress, produced by traumatic events or situations together with inadequate coping skills, is probably an important aetiological factor in many cases of depression (van Praag et al. In Press). Suicidality, thus, might be not so much a feature of depression as such, but rather a consequence of pre-existing personality traits. Personality pathology shows generally little or no response to antidepressants, and hence in that case one cannot expect antidepressants to do suicidality much good.

Suicidality does indeed occur in non-depressed, personality-disordered individuals. This speaks in favour of this hypothesis. On the other hand, if personality pathology were the major cause of suicidality in depression, one would expect suicidal behaviour to occur as frequently in depressive episodes as in states of remission, and this is not what actually happens.

- Social factors

Suicide rates have dropped due to antidepressants but this effect might have been counterbalanced by the impact of social factors. This is a conceivable explanation. Socio-economic environment and prevalence of depression

and suicidality are clearly associated (Hawton et al. 1988; Gunnell et al. 1999). Among the unemployed the risk of suicide is increased, and an inverse relationship has been established between social class and suicide risk (Platt and Hawton 2000). Social circumstances, too, influence the suicide risk. In a small geographical area of Bristol, for instance, Gunnell et al. (2000) found that, over a period of 30 years, social deprivation had risen and so had suicidal behaviour. The relationship reached a statistically significant level. The social deprivation index was based on the sum of Z-scores of four variables: unemployment, car ownership, household overcrowding and house ownership. Hence, it is conceivable that social factors have overridden the beneficial effects of antidepressants on suicide rates. Similarly, improvement in the national economy might have contributed to the decrease in suicide in England and Wales between 1960 and 1997 (McClure 1998).

It is, however, implausible that social deprivation did occur on such a large scale in the developed world that it has overshadowed the beneficial effects of antidepressants, and could explain why these drugs have had such meagre effects on suicidal behaviour.

- Have antidepressants increased suicide rates?

Antidepressants might have boosted suicidal impulses, cancelling out possible positive effects on depression per se. First, they could have energized an anergic patient before mood elevation has commenced, and thus advanced, temporarily, the drive to harm or destroy oneself. This happens sometimes in the early phases of electroconvulsive treatment. The same could happen with antidepressants, particularly if they exert a pronounced stimulating effect on motoricity and level of initiative. Some evidence supports this notion (Damluji and Ferguson 1988; Montgomery 1997).

Another possibility is that antidepressants enhance the suicidal drive directly. A decade ago, a stir was caused by a publication claiming that fluoxetine, a selective serotonin re-uptake inhibitor (SSRI) might increase suicidality in depression (Teicher et al. 1990). Meta-analysis of a large number of studies, however, could not confirm these conclusions. (For review see Healy 1994; Fava and Rosenbaum 1991; Beasley et al. 1991; Walsh et al. 2001.) Yet this notion recently popped up again, when Healy (2000) reported that, in a few normal subjects during treatment with the SSRI sertraline, suicidal tendencies had acutely occurred.

Theoretically, an influence of SSRIs on the regulation of (auto) aggression is certainly conceivable. Both in animals and in humans

serotonin (5-hydroxytryptamine, 5-HT) systems are associated with the regulation of (auto) aggression. Most notably the 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptor-mediated systems are involved. Increasing activity in those neuronal systems will inhibit, decreasing activity will enhance (certain forms of) aggression (Olivier and Mos 1992).

The 5-HT receptors mentioned are located both pre- and postsynaptically. Activation of the postsynaptic receptor leads to activation of the system; activation of the presynaptic counterparts reduce activity in the system.

The immediate effect of an SSRI is to increase availability of 5-HT in the synapse and stimulation of both pre- and postsynaptic 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptors. The net effect on 5-HT-ergic activity will thus be small because pre- and postsynaptic effects will generally cancel out each other. After some time (weeks) SSRIs will desensitize the presynaptic 5-HT<sub>1A</sub> receptor. (It is unknown whether this is also the case with the 5-HT<sub>1D</sub> receptor). This does not happen with the postsynaptic counterpart (Blier and De Montigny 1994). In this way the 5-HT<sub>1A</sub> system gets activated and this effect is considered to be crucial for antidepressant activity. It is, as said, also associated with reduced aggressivity.

If, for whatever reason during a certain period, activation of the presynaptic 5-HT<sub>1A</sub> (and/or the 5-HT<sub>1D</sub>) receptor were to outstrip activation of the postsynaptically located 5-HT<sub>1A</sub> receptor, causing reduction of neuronal activity in the 5-HT<sub>1A</sub> system, theoretically, depressive behaviour might be intensified and (auto) aggressive impulses accentuated, with suicidality as a possible result.

This possibility, however, is for the time being speculative, has not been demonstrated and will be hard to demonstrate in humans.

#### Conclusions

Taking into account that depression is a major suicide precursor and that over the past 20 years antidepressants have been employed on an ever increasing scale, it is puzzling that suicide rates have not dropped accordingly. These observations should be taken seriously, and studied systematically as to the reason why. They should definitely not be swept under the carpet because they do not fit consensus opinions about the treatment of depression prevailing in psychiatry today.

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## Morning Pseudoneutropenia during Clozapine Treatment

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### Summary

*Clozapine, an atypical antipsychotic drug, is associated with a high risk of neutropenia and agranulocytosis, necessitating the immediate discontinuation of the drug. We report the case of a patient who developed clozapine-induced neutropenia. Assessments revealed a pronounced diurnal variation in the number of circulating neutrophils (1200-1900/mm<sup>3</sup> in the morning and 2200-2700/mm<sup>3</sup> in the afternoon). Due to these circadian changes, we decided to continue clozapine treatment.*

**Key words:** transient neutropenia, diurnal variation, clozapine, schizophrenia.

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### Introduction

The dibenzodiazepine derivative clozapine is an atypical antipsychotic that is effective in schizophrenia (Baldessarini and Frankenburg 1991; Pickar 1995). However, between 0.8 and 1% of patients treated with clozapine develop agranulocytosis (Alvir et al. 1993), thus clozapine is only used in schizophrenic patients who are resistant or intolerant to conventional neuroleptics. Given the risk of this life-threatening side effect, patients receiving this drug must follow a stringent haematological monitoring programme to detect blood dyscrasia, which necessitates drug interruption (Gerson and Meltzer 1992).

Neutropenia is also of considerable clinical relevance because it can be either a harmless transient phenomenon or an early sign of incipient agranulocytosis (Hummer et al. 1992). The prevalence of clozapine-induced neutropenia has been estimated to be 2.8% (Lieberman and Alvir 1992). When neutropenia occurs, physicians usually interrupt the treatment and do not reintroduce the drug (Alvir and Lieberman 1994). However, because clozapine is often the last therapeutic option, some physicians are reluctant to stop treatment (Beer et al. 1994), and some authors have suggested alternative practices (Wesson et al. 1996; Murry and Laurent 2001).

We report here the case of a patient suffering from schizophrenia and treated with clozapine. Although this patient developed neutropenia, we decided not to interrupt the treatment.

### Case Report

Mr A. was a 44-year-old Caucasian man suffering from paranoid schizophrenia. He exhibited acute periods with hallucinations, aggressive behaviour and mood variations. Mr A. previously showed resistance to various antipsychotics: conventional neuroleptic medications (e.g. 200 mg/day loxapine, 75 mg/day levomepromazine) as well as risperidone (8 mg/day). Due to associated affective symptoms, he also successively received carbamazepine (interrupted because it induced severe hyponatremia) and valproic acid (2 g/day) in combination with antipsychotics.

Finally, he was given clozapine. The total white blood cell (WBC) and neutrophil counts prior to clozapine initiation were 7100/mm<sup>3</sup> and 5300/mm<sup>3</sup> respectively. Other biological para-

eters, including liver function tests, did not reveal any abnormalities. The dose was gradually increased to 400 mg/day, leading to a satisfactory improvement in symptoms.

A marked and isolated reduction in neutrophil count (1600/mm<sup>3</sup>) occurred 10 weeks after the introduction of clozapine. The neutrophil count remained between 1600 and 1900/mm<sup>3</sup> over the next four weeks and then returned to normal (2200-3100/mm<sup>3</sup>). After 16 weeks of clozapine treatment, the daily dosage was gradually reduced to 200 mg/day (serum level = 229 ng/ml) because the patient complained about excessive sedation. Nineteen weeks after clozapine introduction, the neutrophil count fell to 1500/mm<sup>3</sup> and remained between 1500 and 2100/mm<sup>3</sup> thereafter.

After 27 weeks of clozapine treatment, the neutrophil count further declined to 1300/mm<sup>3</sup>, whereas the total WBC count was in the normal range (4100/mm<sup>3</sup>). As the count was below 1500/mm<sup>3</sup>, we took a blood sample the same day but in the afternoon (at 2 p.m.), and, surprisingly, the neutrophil and total WBC counts were 2200 and 5500/mm<sup>3</sup> respectively. We therefore decided to continue clozapine treatment with a stringent haematological monitoring programme: blood tests were performed twice a week, and whenever WBC counts fell or were below the normal range in the morning (at 8 a.m.) a second test was repeated in the afternoon (at 2 p.m.). During the following weeks, each time the morning neutrophil counts were between 1200 and 1900/mm<sup>3</sup> (WBC counts: 4100-4700/mm<sup>3</sup>), they were between 2200 and 2700/mm<sup>3</sup> in the afternoon (WBC counts: 5400-5800/mm<sup>3</sup>). We considered that as the neutrophil counts were in the normal range in the afternoon, the risk of the patient developing agranulocytosis was low. Thus, we continued clozapine treatment at the same daily dosage (200 mg). After 30 weeks of clozapine treatment, the monitoring no longer revealed any decrease in neutrophil counts.

### Discussion

Transient neutropenia has previously been reported to occur in about 10% of patients treated with carbamazepine or phenothiazines (Mandel and Gross 1968; Pisciotto 1978). The first reports of clozapine-induced transient neutropenia were published in the late 1980s (Lindström 1988; Gaertner et al. 1989; Potter et al. 1989). More recently, transient neutropenia (defined as a return of the neutrophil count to normal values without changing the clozapine dosage) was shown to occur in 22% of 68 patients receiving clozapine for the first time (Hummer et al. 1992). Miller et al. (1997) reported transient neutropenia of short duration (2-5 days), with a spontaneous recovery

following clozapine withdrawal. Weekly benign variations in the WBC count, not necessitating the discontinuation of the drug, have also been reported (Peacock and Gerlach 1994; Lindström 1988). However, our report is only the second that describes such a pronounced diurnal variation in the WBC count during clozapine treatment (Ahokas and Elonen 1999).

Little is known about the complex pathophysiology of granulopoiesis impairment during clozapine treatment. Hummer et al. (1996) hypothesised that successful compensatory mechanisms by cytokines, such as the production of granulocyte colony-stimulating factor (G-CSF), may stimulate granulopoiesis sufficiently in the case of transient neutropenia. Neutropenia may occur in the case of cytokine dysfunction. However, this speculative explanation remains controversial (Schuld et al. 2000). It has also been suggested that prostaglandin E plays a role (Banov et al. 1993).

Diurnal variations in clozapine-induced transient neutropenia are of particular interest. In healthy subjects, circulating blood cells are known to show circadian rhythms (Akbulut et al. 1999). However, little is known about the mechanisms involved in these variations. Haematopoietic growth factors may play a significant role. Indeed, endogenous production of G-CSF has been found to be subject to a diurnal rhythm in both healthy subjects (Jilma et al. 1999; Takeuchi et al. 1996) and neutropenic patients with haematological malignancies (Abdelaal et al. 2000). In the case we describe here, it can be hypothesised that clozapine did not affect the circadian rhythm of G-CSF endogenous production, leading to sufficient compensatory stimulation of granulopoiesis and preservation of the diurnal variation in circulating neutrophils.

Finally, it seems essential, before interrupting clozapine, to determine whether drug-induced neutropenia is transient or malignant. As patients with transient neutropenia are not systematically predisposed to agranulocytosis, interruption of clozapine can be avoided. Laboratory screening tests are being devised to make such a distinction. These tests could include monitoring of endogenous G-CSF levels (Jauss et al. 2000) or the use of a hydrocortisone test (Murry and Laurent 2001). Until these tests become available for routine use, it is necessary to increase the frequency with which WBC counts are determined.

In conclusion, as first suggested by Ahokas and Elonen (1999), when WBC counts fall or are below the normal range, further counts should be repeated on a blood sample taken in the afternoon, before deciding to interrupt clozapine treatment.

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## Comment on the WFSBP Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania

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*I have read the review (World J Biol Psychiatry (2003) 4: 5-13) with interest, but with some disappointment. Despite a masterly appraisal of the literature on anti-manic medication, there was no mention at all of perhaps the biggest challenge in many cases, i.e. whether to discontinue any antidepressant the patient may be taking.*

*I am aware that in some countries it is near-universal practice to do so at the onset of a manic episode. However, for patients who tend to swing into major depression after a manic episode, it may be more sensible to maintain an antidepressant (possibly even if it is this which has caused the manic swing). After all, the manic swing has now occurred, and continued anti-depressant use might help prevent the next depressive episode. Alternatively, one could argue that the continued use of an antidepressant would maintain the manic symptoms. Unfortunately there are, to my knowledge, very few data on which to base such decisions, hence my regret that the review did not examine what evidence exists on this issue.*

Lester Sireling

## Response to Letter to the Editor from Sireling, World J Biol Psychiatry (2003) 4, 195: Comment on the WFSBP Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania

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*Dr Sireling raises an issue which indeed has received but little attention to date, especially as far as conclusive trials to solve the problem are concerned. As a matter of fact, immediate discontinuation of antidepressants is the general practice once a patient becomes manic. As Dr Sireling outlines, the underlying assumption is that continuing anti-*

*depressant medication may kindle and prolong the manic episode. Keeping the often severe impact of a manic episode in mind, discontinuation of antidepressants appears justified. However, due to the fact that it is considered unethical to perform a trial in which manic patients are maintained on antidepressant, this approach has never been supported by scientific evidence. On the other hand, it is also evident that a reasonable number of depressed episodes occur directly following an acute manic episode. Factors promoting these depressed episodes may be a potential depressiogenic effect of classical antipsychotics (as recently observed in a yet unpublished, comparative trial with olanzapine and haloperidol), insufficient efficacy or serum levels of mood stabilisers, and finally, it may be the natural course of the illness. As it usually takes at least a week before the onset of action of any antidepressant, antidepressant treatment would need to be initiated still on the peak of mania to be effective when mania fades and depression may occur. Clearly, no trial has ever been performed administering antidepressants at the peak of mania in order to prevent depression. This is partially different for a mood stabiliser with a strong intrinsic antidepressant component, lamotrigine. In one of the two large lamotrigine maintenance studies, stabilisation with lamotrigine started already as the manic syndrome declined. Compared to placebo, this strategy proved to be an effective treatment in preventing a new depressed episode (Bowden et al. 2003). Thus, despite the absence of conclusive trials, it may be worthwhile to consider adding an antidepressant to the mood stabilizer which is known to have a low switch risk (e.g. SSRIs, bupropion, dopaminergic agents such as pramipexole (Goldberg et al. 1999)) during recovery from mania in selected patients who are known to have a high risk of a consecutive depressed episode.*

*Dr Sireling's remarks are very valuable from a clinical point of view, and, to my regret, there is no clear scientific evidence that leads to a final conclusion. Thus, I would be very interested to hear about readers' experience, illustrated by case studies or observations which may probably also give grounds for a sensible controlled trial to clarify this issue.*

Heinz Grunze

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*Letters published in this Journal do not necessarily reflect the opinions of the Editors or the Editorial Board.*

*Erratum:* The Editorial by Carlos R. Hojajj entitled "Towards a psychiatric biology", published in Volume 1, Number 4 of The World Journal of Biological Psychiatry, was unfortunately printed without page numbers. The full reference for the Editorial is: World J Biol Psychiatry (2000) 1, 170-171. The Journal regrets the error.

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Papers must be written in standard and grammatical English and should present new results as well as be of scientific value. Contributions will be considered for the following categories:

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