

Forms and Frequency of Symptoms and Syndromes in Somatoform Disorders in Different Cultures

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Somatoform disorders are among the commonest and most important psychiatric disorders seen in primary health care facilities (settings) in many parts of the world. Because of cultural factors the frequency and characteristics of symptoms may vary considerably in different countries.

In this paper the forms and manifestations of somatoform disorders in five geographically and culturally diverse countries – Brazil, India, Italy, USA and Zimbabwe – will be presented and compared.

Pharmaco-Economics and Mental Health Policy: A Family Perspective

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Families of persons with severe mental illnesses such as schizophrenia, bipolar disorder and other persistent and disabling disorders are especially concerned with the role pharmaceuticals play in the health economy. In the US most severely mentally ill people find that their illnesses are poorly covered by insurance. Policies are limited in both length and scope of coverage when compared to coverage for other medical illnesses. This discrimination is evident in both public and private insurance and results in poverty and dependency for nearly all persons with severe psychiatric disorders. On a policy level the US health economy is actually a two tiered system, with access based upon income. The neediest, sickest and most at risk for disability are the most poorly served, due to the stigma and discrimination that are at the heart of denial of equitable health insurance. Access to medically necessary treatments is frequently limited. With the introduction of new psychiatric medications, the cruelty of our two-tiered system has become clear. Due to the extremely high price, only a small fraction of the persons who could benefit from clozapine for example, are able to receive it.

State formularies generally restrict access based upon budget constraints. In all states the de factor policy is that cost, not clinical need drives the selection of new medication to be offered to public patients. The practical effect of all this is that families of persons with schizophrenia, who have been vigorous and effective advocates of biomedical research, are forced to pay out of their own pockets for newer medications. Not surprisingly, this situation creates anger and despair. Why are drugs so expensive? Why is the US health economy unable to support subsidy for indigent patients? Why are costs 20% to 50% lower in Europe and South America? NAMI members tell me that the excitement of new drug development is tempered by the realization that the most seriously ill may never receive the benefits. And as we embark upon on massive systemic reform of our health system, the discrimination continues. One parent stated in frustration: "It's like being a child standing with your nose pressed to the glass at the candy counter. You know very well what you want, but you just cannot get it."

Should Depression Be Considered a Lifetime Disorder: Evidence from the Pittsburgh Studies of Maintenance Therapy

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A series of studies carried out at the University of Pittsburgh point strongly to the lifetime nature of recurrent unipolar disorder and to the need for a long-term perspective in the development of treatment strategies. In our initial investigation (Frank et al., 1990), remitted recurrent unipolar patients were randomly assigned to full dose ≈ 220 mg imipramine) maintenance pharmacotherapy, monthly maintenance psychotherapy, the combination or placebo for a period of three years. Full dose medication was highly effective ($p < 0.0001$) in preventing new episodes, with maintenance psychotherapy showing a modest protective effect ($p = 0.05$). In a second investigation (Kupfer et

assignment. A third investigation (Frank et al., 1993), focused on those patients in the original study who had experienced a recurrence in the absence of active pharmacotherapy. Following successful treatment of their recurrence and a 20-week continuation treatment phase, these subjects were randomly assigned to either full or half-dose pharmacotherapy for a three-year period. Full-dose imipramine was associated with fewer recurrences and longer survival time than the half-dose strategy ($p < 0.07$).

Taken together, these studies of recurrent unipolar patients present a picture of a disorder requiring long-term (if not life-long) prophylaxis in a manner similar

al., 1992), subjects who survived the initial three-year trial in one of the two active medication conditions, were randomly assigned to an additional two years of full-dose pharmacotherapy or placebo. Once again, active medication was significantly superior to placebo ($p < 0.006$) in protecting against new episodes, this time in a group of patients who had all previously sustained a remission of almost 3.5 years prior to random

to that apparently required in manic-depressive illness. What remains to be elucidated is: (1) whether more frequent maintenance psychotherapy can provide adequate protection against recurrence and (2) whether there are subgroups of recurrent unipolar patients who can ultimately discontinue treatment without adverse consequences.

GENETICS OF ALZHEIMER'S DISEASE: APP, APOE, AND THE CHROMOSOME 14 LOCUS

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At least three genetic loci can predispose towards AD. These are the APP gene, the ApoE gene and a locus on chromosome 14. Besides summarizing the role of APP mutations in disease pathogenesis, I shall present 4 series of analyses.

- 1) data indicating that ApoE genotype modulates onset age around 55 years in families with APP mutations with ApoE4 causing an earlier, and ApoE2 a later onset age relative to ApoE3.
- 2) data indicating that ApoE genotype does not modulate onset age in families with chromosome 14 locus encoded AD.
- 3) data confirming that ApoE4 shows a strong association with late onset AD.
- 4) genetic information confirming, but not further refining the position of the locus causing very early onset AD located between D14S52 and D14S55.

These data have been generated in collaborations with the Dementia and Prion groups at St. Mary's Hospital, London, the Alzheimer's Group at the Karolinska Institute, Sweden, the Department of Pathology, at the University of Helsinki, Finland and the Alzheimer's Genetic Group at the University of Antwerp, Belgium.

Gene Transfer in Astroglial Cells in a Rat Model of Parkinson's Disease

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Intracerebral transplantation of embryonic dopaminergic cells have shown, in particular, that local striatal restoration of dopaminergic neurotransmission may compensate for sensori-motor impairment associated with the nigro-striatal degeneration in animal models of Parkinson's disease. We are studying gene transfer as a tool to express the neurotransmitter synthesizing enzyme tyrosine hydroxylase (TH) locally in the striatum.

We are exploring both the retroviral system and the adenoviral one, with the aim of comparing their efficiency and safety. Initially, we have constructed two human TH recombinant retroviruses using either the Long Terminal Repeat (LTR) from the Moloney murine leukemia virus or the immediate early promoter from the cytomegalovirus to drive the expression of TH into primary cultures of embryonic striatal cells. Retroviruses only permit the genetic modification through incorporation into chromosomal DNA of dividing cells. We therefore made use of the ability of glial cells to di-

vide in the presence of foetal calf serum or growth factors to allow their infection *in vitro* by the recombinant retroviruses. We could thereby modify up to 100% of glial cells as characterized by their endogenous GFAP, an astroglial marker, as well as the exogenous TH protein expression. The genetically modified astroglial cells were found to release DOPA in a constitutive manner *in vitro*. The functional capacity of the TH-expressing astroglial cells as well as their survival properties were studied after grafting to striatum of rats with 6-hydroxydopamine lesions. Two weeks after transplantation, apomorphine-induced turning was reduced by mean of 60%. TH immunoreactive cells were observed in the denervated striatum three weeks post-grafting. The adenovirus allows the infection of dividing as well as of non-dividing cells such as neurons, resulting in the introduction of recombinant genes in an episomal form. The relative efficiency of this system with that of the retrovirus system will be discussed.