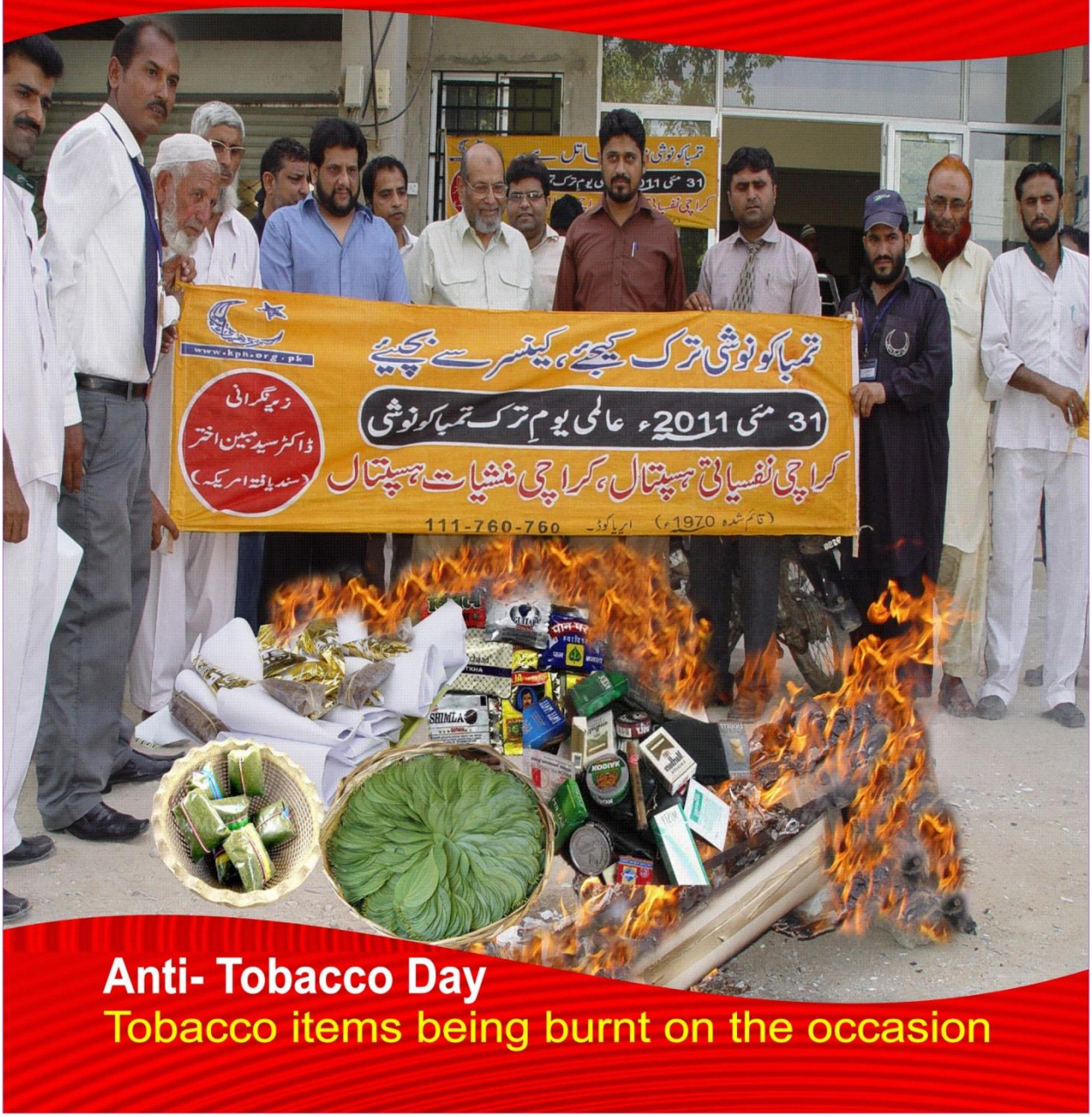
CHIEF EDITOR DR. SYED MUBIN AKHTAR

KARACHI PSYCHIATRIC HOSPITAL

BULLETIN JULY 2011



Anti- Tobacco Day

Tobacco items being burnt on the occasion

Press Conference on the occasion of **Anti-Tobbacco Day**

Tobacco items being burnt on the occasion of **Anti- Tobacco Day**

Karachi Psychiatric Hospital - Meeting of Managers.

KARACHI PSYCHIATRIC HOSPITAL

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MONTHLY BULLETIN

(Psychiatric Research Articles)

جستجوحق کا طریقہ

کسی معاملے میں حق معلوم کرنے کا صحیح طریقہ یہ ہے کہ آدمی شریعت کے اصولوں کو سامنے رکھ کر اُن پر پوری طرح غور کرے۔ اگر غور کرنے سے اس کا دل کسی ایک طرف مطمئن اور یکسو ہو جائے تو اس طریقے کو اختیار کر لے اور اگر تردد باقی رہے تو شرح صدر کے لئے اللہ تعالیٰ سے دُعا کرے اور تلاش و تحقیق میں پوری سرگرمی سے مصروف بھی رہے۔ مجرد دعا پر بھروسا کر لینا اور اپنے فکر و عقل سے کام نہ لینا صحیح شرعی طریقہ نہیں ہے۔

(سید ابوالاعلیٰ مودودیؒ)

Readers are requested to send their articles, comments & suggestions.
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THE CHRONIC MENTAL PATIENT

Prepared by JA Watt, MB, N el-Guebaly, MD

This paper was prepared for the Professional Standards and Practice Council, chaired by Dr N el-Guebaly, and approved by the Board of Directors of the Canadian Psychiatric Association in May 1981.

Definition

For the purpose of this paper, "Chronic Mental Patient" refers to those members of society who suffer from a chronic mental illness and who demonstrate significant impairment of task performance and/or social performance. Often, but not necessarily, the chronic mental patient will have a history of prolonged or frequent hospitalizations for psychiatric treatment. Thus, this group includes the so-called "deinstitutionalized" patients.

A chronic condition is "marked by long duration, by frequent occurrence over a long time, and often by slowly progressing seriousness . . ." Yet we do not consider all persons so afflicted as being chronic mental patients. We can narrow the definition by applying the concept of disability, particularly in terms of vocational and social functioning. We can further sub-divide this group in terms of its use of facilities (institutionalized in psychiatric hospitals, homes for special care, half-way houses, in sheltered employment situations, and so on). A number of efforts have been made to achieve operational definitions in terms of duration of hospitalization, either as an absolute time or percentage of time, number of hospitalizations, and eligibility for social insurance.

Etiology and Prevalence of Chronicity

One might consider etiology from the perspective of the various diagnostic categories which comprise the group of chronic mental patients but a simpler, operational view would be to consider that chronicity results from the limitations of primary preventive measures in the community and their failure to identify illness early and treat it promptly -- secondary prevention. One is then left with the task of reducing the amount of defective functioning left by the disorder and that is tertiary prevention.

Some psychiatric entities, such as various forms of dementia, are unresponsive to known methods of therapy. We have all known, however, patients whose prognosis was considered to be hopeless but who improved and did not join the ranks of the chronic. Sometimes patients fail to get well because they are not treated optimally and that in turn may relate to inadequate evaluation.

Schizophrenia and, less frequently, manic depressive illness contribute heavily to the diagnostic categories found in chronic mental patients. Other significant special groups include the elderly, institutionalized mentally ill, the mentally retarded, emotionally disturbed children and alcoholics, and drug addicts with or without organic brain damage.

There are no accurate figures on the prevalence of the chronic mental patient.

Table 1 from Statistics Canada - Mental Health Statistics provides figures on the distribution of institutionalized patients in various forms of institutions. The total number of institutionalized psychiatric patients in 1975 was reported to be 53,279. We do not know how many of them would fit our definition of the chronic mental patient.

Prevalence of the chronic mental patient in the community is much harder to estimate. Severely mentally retarded and physically handicapped people are easier to identify; particular attention, however, is also to be paid to those individuals recovering from psychiatric illness and Canadian surveys in this area are limited.

Type of Institution	Males	Females
Public mental Hospital	13,569	10,074
Institution for the mentally retarded	11,365	8,533
Public psychiatric Unit	1,530	2,173
Federal psychiatric unit	789	15
Psychiatric Hospital	842	839
Aged and senile home	530	479
Hospital for addicts	369	58
Treatment centre for emotionally disturbed children	1,290	631
Epilepsy hospital (Quebec)	131	62
CANADA	30,415	22,864

Characteristics of the Chronic Mental Patient

Depending on age, diagnosis and other factors, these patients vary greatly in many respects. They do, however, have a number of features in common. Three types of handicapping factors are generally described -- intrinsic, extrinsic and secondary.

Intrinsic or primary factors consist of continuing psychiatric symptoms that are part of the illness itself, for example, thought disorder, delusions, psychomotor retardation. One to two-thirds of discharged chronic schizophrenic patients are significantly disabled by psychiatric symptoms.

Extrinsic factors include premorbid handicaps such as lack of social or vocational skills and intellectual or physical disabilities. A number of studies have demonstrated 20 to 50% of chronic mental patients have no friends and only a minority have any significant community involvement. Those who are married and employed or who have an active social life are much less likely to join the ranks of the chronic mental patient; even when they do enter this category, they tend to function at a higher level than those who are single, unemployed or socially isolated.

Secondary factors represent maladaptive reactions to the illness rather than being part of the illness itself and include loss of self-esteem and self-confidence, helplessness and passivity.

Test and Stein summarized the important characteristics of the chronic mental patient, including a high vulnerability to stress, deficiencies in basic coping skills required for everyday living, extreme dependency, perceiving themselves as quite helpless, difficulty with working in the competitive job market and difficulty with interpersonal relationships. It has been recognized that many of the vocational difficulties of chronic mental patients are, themselves, the result of difficulties in interpersonal relationships but other factors that have contributed include patients' phobic attitudes towards work, fear of failure,

unrealistic attitudes towards work and authority figures and oversensitivity to disappointment or failure.

Cost of Chronicity

The movement to "deinstitutionalize" psychiatric patients gained political support, largely on economic grounds. It was suggested by proponents of the movement to community psychiatry that these patients could be cared for in the community more cheaply than in mental hospitals. It has been shown, however, that only one-fifth of the total cost to the United States of the burden of schizophrenia, by far the most common diagnosis of the chronic mental patient, is represented by the cost of treatment. Two-thirds of the total cost is due to loss of productivity. This enormous loss is due to unemployment, early onset of illness and lack of rehabilitation. Thus, on economic grounds alone, it is obvious that we require to take a second look at this equation and examine the possibility of "making an investment" as a society in the appropriate treatment and rehabilitation of patients suffering from schizophrenia.

As in the case of the elderly, the financial responsibility of maintaining the chronic mental patient in the community places a heavy burden on the individual and his family. In contrast, the government pays the bill if the patient is institutionalized. The difficulty in obtaining adequate financial support has often contributed to the continuation of the "revolving door syndrome". Short-sightedness and a lack of perspective in considering the costs of the care of the chronically mentally ill have resulted often simply in a transfer of costs from one compartment of the public purse to another, including the prison system. In Canada, federal-provincial cost-sharing arrangements have contributed to this phenomenon.

Too often we fail to recognize the non-financial costs of mental illness - the pain and suffering of the afflicted and of their families. Menuck quoted from an editorial in the British Medical Journal: "You can put him in a back ward for the rest of his days and then you have written him off, his life is finished. Or you can have him at home, and then you have to accept that you will have to alter your whole life. You will never be free again." He went on to observe, "It is not surprising that families of chronic patients often resist efforts at rehabilitation." A well-organized program, providing group support to the parents and families of schizophrenic patients has been shown to produce not only a great decrease in resistance of families but also mobilization of additional support on behalf of the disabled patient.

Other reports have shown that a comprehensive community- based treatment program for the chronically disabled psychiatric patient achieved not only a marked reduction in the use of hospitalization but also a better adjustment to the community than was attained by patients treated conventionally using progressive short-term hospitalization plus aftercare. The cost of treatment was ten percent greater for the model program than for the hospital-based treatment but resulted in greater productivity and other benefits which out-weighed the extra costs. No difference was found in the burden to the family and the community between the two approaches. This was attributed to

"the enormous amount of support" given to the patient, family and community in the model program. The benefits to the patient of the community-based program were lost when the special programming was discontinued.

Attitudinal Difficulties

Our attitudes and abilities to solve a problem may be largely determined by the ways in which we conceptualize and define it. A major obstacle to the successful rehabilitation of many chronic mental patients lies in the attitudes in society which are reflected in the political, economic, professional and familial decisions which impinge upon the life of the chronic patient. When institutionalization was the accepted approach, the ability of patients to provide for their own needs was under-estimated and the prognosis accorded them excessively pessimistic. The movement towards deinstitutionalization recognized that bias and replaced it with another equally wrong bias so that often the legitimate needs of patients were overlooked and they were removed from the relative safety of the mental hospital and placed in the "community" without adequate resources. The Group for the Advancement of Psychiatry has documented the distressing frequency with which chronic mental patients may be living in a community but in no sense can be considered members of the community.

The more one studies this problem, the more one appreciates its bewildering complexity. This very complexity is probably the greatest obstacle to appropriate, individualized treatment of the chronic mental patient. When faced with an excessively complex, apparently contradictory set of problems, our reactions tend to be maladaptive and we fail to achieve satisfactory resolution of the problem. Thus, one sees in society, in the patients themselves and their families, despair, pessimism and prejudice. Professionals share in those attitudes and try to master the complexity by over-simplification which fosters psychiatry's traditional error -- the "band wagon" approach.

Society, including the professionals involved, periodically "rediscover" the plight of the long-term severely mentally ill. In the 19th century, reformers shocked by conditions of the mentally ill in the community, fought for humane hospitalization. Within a few decades, mental patients were forgotten and became warehoused in the depersonalizing atmosphere of huge, segregated hospitals. The result was an outcry to shift these patients back to the community. We are now facing the backlash of having done so without providing supportive services in the community, resulting in a new segregation of the mentally ill, this time in our downtown ghettos.

We should consider seriously the advice of J.K. Wing: "Meanwhile, however, it might be best to call a moratorium on the kind of claim that suggests that any single factor (such as the harmful effects of institutions, or the malevolence or incompetence of relatives, or the manipulations of psychiatrists on behalf of the `establishment', or the inadequate prescription of physical methods of treatment) is chiefly responsible, for the continued development of long-term handicap."

Rehabilitative Considerations

A. In Caring For The Individual:

1. Individual Evaluation and Identification of Specific Goals

To try to decrease the stigma associated with chronic mental illness and the negative effects of labeling, one might link this phenomenon to equivalent situations in other areas of medicine. The emphasis should be, not on the duration of dysfunction (elapsed or anticipated), but on the nature and extent of the disability. As more potent and specific forms of treatment become available, accuracy in diagnosis becomes more important. Thus, while it continues to be essential not to miss a treatable organic condition, we now recognize more clearly the importance of differentiating affective disorders from schizophrenia and dementia.

In addition, each patient requires careful study which goes beyond the formal psychiatric diagnoses and which identifies the strengths and weaknesses of the patient. A problem- oriented approach or rehabilitation diagnoses identifying skill deficits that prevent the patient from functioning in society is also required. We need to devise more comprehensive methods of evaluation that address themselves to the many areas of functioning which we know are frequently deficient. Many instruments exist and are now used as research tools but could be adapted to clinical use.

2. Specificity of Treatment: The Benefits and Limitations of the Individual Versus Group Approach

Individual evaluation of patients does not necessarily assume individual treatment. It is possible to meet the specific needs of the individual on a group basis. To achieve this, we need a large enough pool of patients from which to select. This underscores one of the advantages of the mental hospital over the small psychiatric unit in a general hospital which can never hope to provide such a wide range of therapeutic programs.

Many living-skills programs have now been devised. The more specifically programs can be directed to meeting the needs of patients, the more successful we can hope to be. Such programs should be a required part of the therapeutic armamentarium of the psychiatric hospital and should be available to both inpatients and outpatients.

"Total psychosocial programs" have been shown to be effective in helping rehabilitate many chronic mental patients. The individual techniques used in such programs are clearly of benefit but we question the emphasis on "total". If we are to be efficient and economical in rehabilitation, we must be more specific. An analogous approach in general medicine might be to give to all patients, a cocktail of Penicillin, iron and vitamins. Such an approach is unlikely to be accepted in modern medicine and yet all too often is still offered in psychiatry.

3. Monitoring Medication and Patient Compliance

Follow-up programs should include medication monitoring with emphasis on prescribing practices and patient compliance. It is well known that a major factor in the relapse of patients suffering from schizophrenia is failure to take psychotropic drugs. Careful attention

must be paid to dosage and side effects and every effort made to ensure that the patient appreciates the implications of taking or not taking his medication.

B. Mobilizing Community Resources:

1. Range of Services

The chronic patient in a mental hospital could count on being fed, clothed, sheltered and on having access to basic medical care. If patients are to survive in the community, they must be guaranteed these essential resources.

A comprehensive system of services must be provided for chronic mental patients in the community. The services should be designed to meet the patient's hitherto unmet needs but should not meet needs which the patient can meet himself. Support systems should not reinforce dependency, passivity, apathy and chronicity but instead should encourage continuing efforts to achieve self-sufficiency. A wide range of living situations should be made available to provide humanely for the unmet needs of the chronic patient. There should be potential for movement within that system through a series of small increments in complexity and stress to encourage increasing movement toward the maximal degree of social inter- dependency of which the patient is capable.

In addition to publicly funded programs, many excellent support systems focusing on the needs of specific groups are available on a mutual self-help basis (for example, Alcoholics Anonymous, Recovery Incorporated, and others). In addition, volunteer organizations have been formed by the relatives or friends of the afflicted with the intention of helping the disabled person and those close to him (Mental Health Canada, Friends of Schizophrenics). Such efforts are to be strongly encouraged.

2. Funding Mechanisms

Ideally, adequate funding for the care of the chronic mental patient should follow him from the institution to the community. The present diversity and fragmentation of sources of funding involved in the care of these patients is a major barrier to the patient's rehabilitative process. One suggestion has been a voucher system whereby the program rendering the system could be reimbursed for it by a central source whose funds are relatively stable.

We must consider the usual deployment of resources in which we provide more and more psychiatric help to the less severely disabled and less and less to the more disabled. Early and accurate diagnoses coupled with energetic treatment are essential. The inevitable residuum of disability occurring, however, must not be neglected.

In any new Federal-Provincial agreement of allocation of health dollars, some monitoring system should exist to ensure adequate funding of this defenseless segment of the population across the nation.

3. Administrative Leadership

A single administrative structure should be responsible for planning and integrating services within a given geographic area. Lines of responsibility and authority should be clear. Reports on such relatively autonomous services concur regarding the importance of developing a care system whose only

mandate is the care of the chronically mentally ill.

4. Manpower Adequacy -- Quality and Quantity

The relatively low prestige and status bestowed upon professionals involved in chronic care, coupled with the difficult nature of the work itself have contributed to severe manpower shortages at all professional levels in the field and resulted in the delegation of more and more complex professional responsibilities to less and less adequately trained workers, leading to an erosion of the care provided. As a result of the manpower deficiencies experienced in most provincial psychiatric hospitals, several university residency training programs have withdrawn their trainees, leading to a subsequent output of psychiatrists untrained in the field of chronic care and therefore to qualified psychiatrists avoiding this unfamiliar field. To help break the vicious circle, it is recommended that adequate training indicated for the chronically mentally ill be a specific required component of residency training in psychiatry while ensuring that proper supervision of this training is provided. The same deficiencies in the undergraduate medical curriculum must also be corrected.

In 1978, a telephone survey regarding U.S. state mental hospitals elicited the following ten strategies most often used successfully in order of frequency to attract psychiatrists (36): 1. competitive salaries, 2. university relationships, 3. state's living conditions, 4. active recruitment programs, 5. quality of residency programs, 6. fringe benefits, 7. obligatory jobs, 8. part-time private practice, 9. quality of treatment programs, 10. jobs in innovative care systems.

5. Vocational Supports -- Development of Coping Skills

The needs, capacity and ability of the individual patient for education and training must be carefully assessed. Programs should offer a continuum of prevocational, vocational and educational and recreational rehabilitation. Acquisition of daily living skills and participation in social amenities must be stressed. An energetic job-finding and placement service for the chronically mentally ill is the necessary final component of an adequate system of rehabilitation. The positive association between successful outcome and the treatment of schizophrenia and the ability of the patient to work has long been recognized. While acknowledging that prolonged hospitalizations had a negative effect on the ability of schizophrenic patients to function, Price observed that a prolonged absence from regular employment in the community had at least as great an effect. A recent study of St. Wulston's, a rehabilitation hospital in England, specializing in the treatment of chronic mental patients who have had a minimum of eight years and an average of sixteen years in hospital, reported that of a group of patients treated there ten years earlier, "65% have been self- sufficient for about a decade."

6. Continuity of Care and Personal Follow-up

The frequency of relapse and readmission of patients suffering from

chronic mental illness is substantially reduced if continuity of care is provided with ongoing personal follow- up. One of the characteristics of the chronic mental patient is his inability to cope easily with change. Transitions and transfers must be well planned and co-ordinated. Hospitals and community programs should have shared liaison workers and teams. It is essential that each patient have available a resource person who will continue to work with him and guide and support him throughout inpatient and outpatient treatment and rehabilitation. Recognition of this need has seen the emergence of the primary therapist or case manager. Unfortunately, the uncritical adoption of this approach has resulted in the allocation of inadequately trained staff to the supervision of patients. To abandon our most disabled citizens to treatment by our least skilled caretakers is self-defeating. Appropriate recognition of the respective skills of the different professional disciplines is essential. While much of the work with the chronic mental patient may be appropriately delegated, psychiatrists must maintain their responsibility to supervise such care.

7. Maintenance of Motivation and Patient Advocacy

Usually before someone seeks help, he has "given up" on his ability to maintain a particular level of functioning without assistance. For the chronic mental patient and often for his family, giving-up may become almost a way of life. Each defeat erodes motivation and we must provide support in such a way that the patient knows he is not alone and his ability to solve problems is enhanced. This again underscores the importance of a personal relationship with the patient which is so often absent when follow-up care is given simply in the context of a clinic approach to medication monitoring.

The term "advocacy" is not used in this paper to imply an adversarial concept but is a reminder that an essential component of the work of the case manager is to help the patient learn to cope with the complex bureaucracies involved in his care.

In some cases, this will include an acceptance that the patient may not be able to achieve self-sufficiency. Patients should be given every opportunity to lead as meaningful lives as possible, within the limits of their disabilities and attention should be paid to their recreational needs. We must try to maintain as enriched a social environment for each patient as is possible and appropriate. Thus, every effort should be made to strengthen appropriate links with family and friends. Volunteers, suitably trained and supported, may play a valuable role.

8. Hospitalization

Even the most effective community program will be inadequate to deal with certain crises such as imminent suicidal or homicidal risk, very severe psychotic illness and complicated psychiatric and medical problems. In such situations, access to hospitalization must be assured.

Without falling into the trap of the self-fulfilling prophecy, we must also face the reality that some patients will continue to require "asylum" and that even when they have attained their full potential they may not be competent to live in the community. Our administrative decisions regarding patients must be tempered with

humanity.

9. A Patient's Bill of Rights

Legislative concerns over the mentally ill and particularly the institutionalized subgroup has taken, recently, various forms. An extensive literature is available on this subject including consumers' opinions. The major issues involved include:

a) the individual's right to freedom versus the right to treatment -- the debate over the issues surrounding the commitment of the mentally ill are of relevance to the rights of the chronically mentally ill. While abuses in the commitment process are to be deplored, the Canadian Psychiatric Association stands firmly behind the right of the individual to receive treatment when ill.

b) the right to consent to treatment and the right to refuse it -- issues surrounding consent have recently been the subject of a position paper of the Canadian Psychiatric Association in favour of obtaining free, full and informed consent, insofar as this is possible.

c) the right to confidentiality of personal records -- the present debate centres around the right of the individual to have information concerning his condition remain confidential versus the often legitimate needs of treatment professionals and some of society's organizations to have access to his records. Once more the Canadian Psychiatric Association is on record as favouring securing consent insofar as this is possible and has recently adopted a new position paper regarding the safety of computerized records advocating the use of specific health identifiers for all personal medical records.

d) the right to economic benefits -- the former practice of employing residents in institutions to perform productive labour associated with the maintenance of these institutions without adequate compensation is no longer acceptable. The rationale proposed include the need to solve the financing and staffing shortages of the organization and the difficulty in distinguishing between work of benefit to the institution and work for the benefit of the person. There is a major need for further legislation to prohibit discrimination in terms of rights, benefits and privileges for the mentally handicapped.

e) the right to a humane, psychological and physical environment -- the provision of an environment that promotes dignity and self respect is one of the rights of the chronic mental patient and one of the goals of this brief.

f) the right to information -- the right to participate in the decision-making process involving his care is another essential aspect of the patient's rehabilitation. Accurate information regarding his status and the resources available to him facilitate this participation.

10. Community Education

The biggest challenge in the field is that of changing the community's attitudes. We know from our experience with tuberculosis, for example, that major shifts in attitude are likely to occur only in response to the development of

successful prevention and/or therapy. In the meantime, we must continue such efforts as in the use of the media to improve the image of the mentally ill, the use of community volunteers and integration and acceptance into neighbourhoods including prohibiting zoning discrimination, education and consultation to relatives and enhancement of the prestige and status of the caretaker involved in the area.

11. Ongoing Evaluation and Research

A successful community network must be the subject of ongoing evaluation. At the federal level this evaluation can be encouraged through the development of national standards. At the provincial level standards for involved facilities can be further developed along with guidelines for the licensing of workers in the field and the provision of competitive working conditions.

There must be a continuing emphasis on research in the area of the chronic mental patient including epidemiology, etiology, therapy, model programs, outcome and effective service delivery.

Summary of Recommendations

The Canadian Psychiatric Association recommends:

1. In this International Year of Disabled Persons, that the needs of the chronic mental patient be publicized with emphasis on the potential for improvement if these needs are adequately met. A working definition of the chronic mental patient refers to those members of society who suffer from a chronic mental illness and who demonstrate significant impairment of task performance and/or social performance.
2. A comprehensive network of services should be developed including provision for basic needs with a range of housing options, inpatient and outpatient psychiatric evaluations and treatment, personal clinical support, living-skills training and vocational assessment and training. Aside from patient needs, the professional status of the caregivers involved is to be enhanced. Laudable efforts by self-help groups should be further encouraged.
3. Community resources should be enlisted following principles and practices identified as basic to successful programs already existing, for example:
   - provision of economic stability
   - presence of administrative leadership
   - striving for continuity of care
   - allowance for adequate manpower
   - establishment of vocational supports
   - respect for patients' rights
   - provision of community education
   - design of ongoing evaluation and research
4. A greater emphasis should be placed in undergraduate and postgraduate medical and psychiatric training programs on the treatment of the chronically ill.
5. The Canadian Council on Hospital Accreditation should continue to elaborate and publish criteria by which services to the chronically mentally ill would be evaluated both at the inpatient and outpatient levels. These criteria when available should be promoted in all relevant institutions.

PREVALENCE AND CORRELATES OF BIPOLAR SPECTRUM DISORDER IN THE WORLD MENTAL HEALTH SURVEY INITIATIVE

Merikangas KR et al - Arch Gen Psychiatry 2011 Mar

Bipolar disorder causes more disability than cancer, epilepsy, or Alzheimer disease. To determine the worldwide prevalence of bipolar I disorder (BP-I), bipolar II disorder (BP-II), and subthreshold bipolar illness (having 1 manic symptom but not meeting full hypomania criteria), researchers gave 61,392 adults structured diagnostic interviews in their homes in 11 countries on 5 continents.

Overall, lifetime and 1-year prevalences were 0.6% and 0.4% for BP-I, 0.4% and 0.3% for BP-II, and 1.4% and 0.8% for subthreshold bipolar illness. Lifetime and 12-month rates of all bipolar disorders were highest in the U.S. (4.4% and 2.8%, respectively). Approximately 76% of participants within the bipolar spectrum also met criteria for another lifetime disorder, with 44% having three or more comorbidities, most commonly anxiety disorders (especially panic attacks). Although severe combined symptoms and suicidality increased from subthreshold bipolar illness to BP-II to BP-I, severe and moderate role impairment were similar in all subtypes (29%-57%). In those with subthreshold bipolar illness, 36% reported suicidal ideation in the past year, 15% had a plan, and 10% had made an attempt. Even in high-income countries, only half of bipolar subjects had ever been treated by mental health specialists (BP-I, 61%; BP-II, 71%; subthreshold bipolar, 37%).

Comment: It is striking that subthreshold bipolar disorder is associated with a much higher rate of suicidality than is seen in the general population and that it involves as much role impairment as franker forms of bipolar disorder. Milder bipolar disorders, therefore, should be treated aggressively, although patients with milder forms do not receive such treatment as frequently as those with more obvious bipolar subtypes. The high rate of comorbid anxiety and substance use disorders indicates that clinicians should carefully screen anxious and substance-using patients for bipolar disorder.

http://psychiatry.jwatch.org/cgi/content/full/2011/425/1

WRESTLING WITH BIPOLAR DISORDER

Dr. Ghaemi

It's one of the most missed diagnoses in psychiatry. Bipolar disorder, involving moods that swing between the highs of mania and the lows of depression, is typically confused with everything from unipolar depression to schizophrenia to substance abuse, to borderline personality disorder, with just about all stops in between. Patients themselves often resist diagnosis, because they may not see as pathologic the surge in energy that accompanies the mania or hypomania that distinguishes the condition.

But on a few points consensus is emerging. Bipolar disorder is a chronically recurring illness. And the age of onset is dropping-in less than one generation it has gone from age 32 to 19. Whether there is a genuine increase in prevalence of the disorder is a matter of some debate, but there does seem to be a genuine increase among the young.

What's more, the depression of manic-depression is emerging as a particularly thorny problem for both patients and their doctors.

Depression is the bane of treatment of bipolar disorder.

It's what is most likely to motivate patients to accept care. People spend more time in the depression phase of the disorder. And unlike unipolar depression, the depression of bipolar illness tends to be treatment-resistant.

Antidepressants don't work very well in bipolar depression. They are underwhelming in their ability to treat the depression. In fact, a shift away from antidepressants is formally recognized in new treatment guidelines for bipolar disorder.

As physicians gain experience in treating the disorder, they are discovering that antidepressants have two negative effects on the course of the disorder. Used by themselves, **antidepressants can induce manic episodes. And over time they can accelerate mood cycling, increasing the frequency of episodes of depression or of mania followed by depression.**

Instead, research points to the value of drugs that work as mood stabilizers for the depression of bipolar disorder, either alone or in combination with antidepressants. If antidepressants have any use at all in bipolar disorder, it may be as acute treatment for bouts of severe depression before mood stabilizers are added or substituted.

Even in cases of severe depression, the new guidelines favor increasing the dosage of mood stabilizers over other strategies.

Not so long ago, mood stabilizers could be summed up in a single word-lithium, in use since the 1960s to tame mania. But research has additionally demonstrated the effectiveness of divalproex sodium (Depakote) and lamotrigine (Lamictal), drugs that were initially developed for use as anticonvulsants in seizure disorders. Divalproex sodium has been approved for use as a mood stabilizer in bipolar disorder for several years, while lamotrigine is undergoing clinical trials for such an application.

Optimizing the dose of lithium or

divalproex has good antidepressant effects. We also now know that divalproex and lamotrigine are very good for preventing recurrence in bipolar patients. A study showed that lamotrigine not only delays the time to any mood events but is notably effective against the depressive lows of bipolar illness.

No one knows for sure exactly how anticonvulsants work in bipolar disorder. For that matter, the condition has been described since the time of Hippocrates, but it is still not clear what goes awry in manic-depression.

Despite the unknowns, medications for treating the disorder are proliferating. In contrast to downplaying antidepressants in the depressive phase of the disorder, clinical research is ramping up the value of antipsychotic drugs for combating the manic phase, albeit a new generation of such drugs, collectively called atypical antipsychotics. Chief among them are olanzapine (Zyprexa) and risperidone (Risperdal). They are now considered a first-line approach to acute mania, and adjuncts for long-term therapy along with mood stabilizers.

In the long term, however, medication goes only so far. Drugs are not effective enough. It may have to do with the overuse of antidepressants; they interfere with the benefits of mood stabilizers.

Medications don't take you to the finish line. There seem to be residual symptoms of depression that don't clear. Even when patients stabilize into a normal, or euthymic, mood state, he says, some troubling signs can appear.

Sometimes we see in euthymic patients cognitive dysfunction that we didn't expect in the past-word-finding difficulties, trouble maintaining concentration.

Cumulative cognitive impairment seems to emerge with time. It may be related to findings of decreased size of the hippocampus, a brain structure that serves memory. We are on the verge of recognizing long-term cognitive impairment as a result of bipolar disorder.

There is a role for aggressive psychotherapy for keeping patients well, for keeping everyday ups and downs from becoming full-blown episodes. At the very least, psychotherapy can help patients resolve the work and relationship problems that often outlast symptoms.

In addition, psychotherapy can help patients learn new coping styles and interpersonal habits. **Many of the ways patients deal with their illness are not relevant when they are well.**

For example, many people develop the habit of staying up late as a way of coping with the manic symptoms. "What they couldn't change before because of the illness needs to be changed after treatment if, for example, it bothers a spouse. People have to learn to change. But the longer one is ill, the harder it is to become completely well, because the harder it is to change the habits of one's life."

And for young people diagnosed with bipolar illness, he considers psychotherapy essential. The younger patients are, the less convinced they are that they have bipolar disorder. They have impaired insight. They're especially concerned about the need to take medications. They should be in psychotherapy to get educated about the illness and medication.

The value of support groups, especially for young people is stressed. It's another, important layer of validation.

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http://www.psychologytoday.com/node/24939

SILENT BRAIN INFARCTS, LEUKOARAIOSIS, AND LONG-TERM PROGNOSIS IN YOUNG ISCHEMIC STROKE PATIENTS

Pataala J, et al, - Neurology 2011

MRI-identified silent brain infarcts and leukoaraiosis in first-ever ischemic stroke patients younger than 50 years were prognostic for longer-term adverse outcomes, according to a long-term study.

Of the 655 patients (mean age 40) followed for a mean of 8.7 years, multiple silent brain infarcts independently raised the risk for recurrent ischemic stroke (odds ratio 2.48; 95% CI 1.24-4.94) adjusted for age, gender, risk factors, stroke etiology, and leukoaraiosis. After further adjustment for initial stroke severity and presence of silent brain infarcts, moderate to severe leukoaraiosis increased the risk for death (OR 3.43; 95% CI 1.58-7.42).

Of the 86 patients with silent brain infarcts, 46 had single and 40 had multiple infarcts. In the 50 patients with leukoaraiosis, 21 were classified as mild, 27 as moderate, and two as severe. Both 1.5T and 3T MRI scanners were used in the study.

Leukoaraiosis, or periventricular white matter disease, is a term for changes in the cerebral white matter. Silent brain infarcts and leukoaraiosis are common findings in older individuals free of cerebrovascular disease and among patients with stroke. Both are mainly associated with small-vessel disease pathology.

Putaala and colleagues noted that previous studies, showing an association between leukoaraiosis and adverse outcomes, have not included substantial numbers of young people.

Their observational cohort study included consecutive MRI-scanned patients, ages 15 to 49, at Helsinki University Central Hospital from 1994 through 2007.

Outcome measures were nonfatal or fatal ischemic stroke, composite vascular endpoint, and death from any cause.

Researchers reported that the follow-up time amounted to a total of 5,439 years of observation. Follow up was at least five years for 75.1% and at least 10 years for 35% of the patients.

Investigators recorded the following:

- Seventy nonfatal ischemic strokes
- Two fatal ischemic strokes
- Ten hemorrhagic strokes
- Twenty-seven myocardial infarcts or other arterial events

Overall, 119 patients had some vascular event (composite vascular endpoint) and 61 died.

The cumulative risk for recurrent ischemic stroke was significantly higher in patients with silent brain infarcts than in those without (P<0.001). Risk for recurrent ischemic stroke was higher in those with leukoaraiosis than in those without (P<0.037).

Also associated with risk of nonfatal or fatal recurrent ischemic stroke, after a univariate Cox proportional hazards analysis, were increasing age, hypertension, both types of

diabetes, and large-artery atherosclerosis underlying the index stroke.

The risk for the composite vascular endpoint was higher in patients with silent brain infarcts than in those without them (P<0.003), but no statistically significant difference emerged between those with and without leukoaraiosis (P<0.088).

Univariate associations with the composite vascular endpoint included increasing age, male gender, smoking, hypertension, cardiovascular disease, both types of diabetes, and large-artery and small-vessel disease underlying the index stroke.

Researchers observed no difference in mortality between patients with or without silent brain infarcts (P<0.054), whereas a significantly increased long-term risk of death afflicted those with leukoaraiosis compared to those without leukoaraiosis (P<0.001).

Also associated with long-term mortality were increasing age, hypertension, cardiovascular disease, history of TIA, type 1 diabetes, heavy drinking, severe index stroke (NIHSS ?15), and large-artery atherosclerosis.

"Since silent brain infarcts and leukoaraiosis seem to be prognostically relevant, and because they are more sensitively detected with MRI than with CT, MRI should be the primary imaging method of choice in all eligible young patients with stroke.

Limitations of the study include its observational nature, the low number of patients with leukoaraiosis, and the homogeneity of patients, who were mostly Caucasian.

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http://www.medpagetoday.com/Neurology/Strokes/26598?utm_content=&utm_medium=email&utm_campaign=DailyHeadlines&utm_source=WC&userid=238322

EFFICACY OF DRUG TREATMENTS FOR GENERALISED ANXIETY DISORDER: SYSTEMATIC REVIEW AND META-ANALYSIS

D Baldwin, et al BMJ

ABSTRACT

OBJECTIVE to appraise the evidence for comparative efficacy and tolerability of drug treatments in patients with generalised anxiety disorder.

DESIGN systematic review of randomised controlled trials. Primary Bayesian probabilistic mixed treatment meta-analyses allowed pharmacological treatments to be ranked for effectiveness for each outcome measure, given as percentage probability of being the most effective treatment, secondary frequentist mixed treatment meta-analyses conducted with random effects model; effect size reported as odds ratio and 95% confidence interval.

DATA sources Medline, Embase, Biosis, PsycInfo, health economic evaluations database, national health service economic evaluation database, and database of abstracts of reviews of effects via datastar, and cochrane database of systematic reviews via cochrane library (January 1980 to February 2009).

ELIGIBILITY CRITERIA double blind placebo controlled randomised controlled trials; published systematic reviews and meta-analyses of randomised controlled trials. randomised controlled trials including adult participants (aged greater than or equal to 18) receiving any pharmacological treatment for generalised anxiety disorder.

DATA ABSTRACTION methods titles or abstracts reviewed initially, followed by review of full text publications for citations remaining after first pass. A three person team conducted screening; an independent reviewer checked a random selection (10%) of articles screened. data extracted for meta-analysis were also independently reviewed.

MAIN OUTCOME MEASURES proportion of participants experiencing greater than or equal to 50% reduction from baseline score on Hamilton anxiety scale (ham-a) (response), proportion with final ham-a score less than or equal to 7 (remission), proportion withdrawing from trial because of adverse events (tolerability).

RESULTS the review identified 3249 citations, and 46 randomised controlled trials met inclusion criteria; 27 trials contained sufficient or appropriate data for inclusion in the analysis. Analyses compared nine drugs (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine). In the primary probabilistic mixed treatment meta-analyses, fluoxetine was ranked first for response and remission (probability of 62.9% and 60.6%, respectively) and sertraline was ranked first for tolerability (49.3%). In a subanalysis ranking treatments for

generalised anxiety disorder currently licensed in the united kingdom, duloxetine was ranked first for response (third across all treatments; 2.7%), escitalopram was ranked first for remission (second across all treatments; 26.7%), and pregabalin was ranked first for tolerability (second across all treatments; 7.7%).

CONCLUSIONS though the frequentist analysis was inconclusive because of a high level of uncertainty in effect sizes (based on the relatively small number of comparative trials), the probabilistic analysis, which did not rely on significant outcomes, showed that fluoxetine (in terms of response and remission) and sertraline (in terms of tolerability) seem to have some advantages over other treatments. Among five UK licensed treatments, duloxetine, escitalopram, and pregabalin might offer some advantages over venlafaxine and paroxetine.

DELIRIUM IN ELDERLY PATIENTS AND THE RISK OF POST DISCHARGE MORTALITY, INSTITUTIONALIZATION, AND DEMENTIA: A META-ANALYSIS

Witlox J et al -JAMA 2010

Delirium in patients with dementia accelerates cognitive deterioration. How are elders without dementia affected by an episode of delirium? In a meta-analysis, researchers examined whether delirium in patients 65 or older was associated with poor outcome, independent of comorbid illness or dementia. The authors examined studies from 1981 to 2010 with mean or median age 65 or older, quantitative data on outcome, and at least 3 months of follow-up. Of the initial 2939 articles screened, 42 met all criteria, and researchers analyzed 12 for mortality, 7 for institutionalization, and 2 for dementia outcomes. Secondary analyses examined unadjusted stratified risks in 38 studies.

Primary analyses used data adjusted for age, sex, illness severity, and comorbidities. Delirium was associated with significantly increased risks for death (38.0% in patients with delirium vs. 27.5% in patients without delirium; average follow-up, 22.7 months), institutionalization (33.4% vs. 10.7%; average follow-up, 14.6 months), and dementia (62.5% vs. 8.1%; average follow-up, 4.1 years). Secondary analyses confirmed that these associations persisted independent of preexisting dementia.

Comment: Delirium in older patients is a serious condition with significant morbidity and mortality. Interestingly, the authors did not control for the use of antipsychotic medications, which can have poor effects in older patients. It is evident that as a group, seniors with delirium are already at high medical risk. Do antipsychotic drugs modify the risk in this population? Or do the risks attributed to antipsychotics actually stem from the disorder?

http://psychiatry.jwatch.org/cgi
/content/full/2010/913/5

CARBAMAZEPINE-INDUCED TOXIC EFFECTS AND HLA-B*1502 SCREENING IN TAIWAN

Chen P et al N Engl J Med 2011 Mar 24

Carbamazepine - an anticonvulsant, mood-stabilizing drug, and analgesic agent for trigeminal neuralgia - can cause various drug reactions, ranging from exanthema to severe blistering reactions. Two new studies address the value of genetic testing for predicting or avoiding such reactions.

In certain Asian populations, carbamazepine is the most common cause of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) - which are potentially life-threatening - and such reactions are strongly associated with the HLA-B*1502 allele (odds ratio, 1357, for carriers vs. noncarriers). Chen and colleagues tested for the HLA-B*1502 allele in 4855 Taiwanese patients with indications for carbamazepine use. They advised the 372 carriers against starting carbamazepine. (Five carriers were lost to follow-up.) During a 2-month follow-up, no participant developed SJS or TEN, compared with the 10 cases that could be expected based on historical controls. However, milder reactions developed in some carriers and noncarriers.

McCormack and colleagues examined the association of the HLA-A*3101 allele with carbamazepine-induced reactions among people of Northern European ancestry. In a comparison of 145 participants with carbamazepine-induced reactions (including those with SJS-TEN and those with less-severe reactions) and 257 controls without adverse drug reactions, toxic reactions were strongly and significantly associated with the HLA-A*3101 allele (OR, 9.12). Testing for the presence of HLA-A*3101 had a sensitivity of 26% and a specificity of 96% for identifying those with carbamazepine-associated reactions. The authors estimate that a positive test would increase the probability of a reaction from about 5% (without genetic testing) to 26%, whereas a negative test would reduce the probability to 3.8%.

Comment: The findings of these two well-designed studies suggest that consideration should be given to the presence of HLA-B*1502 and HLA-A*3101 as risk factors for carbamazepine-induced toxic effects in Asian and European populations. The tests for these alleles are available for clinical use and can be used in these populations. Additional studies in populations of different ancestry are required before the test should be considered in non-Asian and non-European patients. Further research may also provide insights into how these alleles increase the risks for the various forms of carbamazepine reactions. In 2007, the FDA formally recommended testing for the HLA-B*1502 allele in patients of Asian ancestry, including South Asian Indians, before starting carbamazepine therapy.

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http://neurology.jwatch.org/cgi/content/full/2011/323/1?

NO BIRTH DEFECTS DUE TO ANTILEPTICS (EXCEPT TOPIMARATE) J.A.M.A

ABSTRACT

CONTEXT Epilepsy during pregnancy is a therapeutic challenge. Since the 1990s, the number of licensed antiepileptic drugs has substantially increased, but safety data on first-trimester use of newer-generation antiepileptic drugs and birth defects are limited.

OBJECTIVE To study the association between fetal exposure to newer-generation antiepileptic drugs during the first trimester of pregnancy and the risk of major birth defects.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study of 837 795 live-born infants in Denmark from January 1, 1996, through September 30, 2008. Individual-level information on dispensed antiepileptic drugs to mothers, birth defect diagnoses, and potential confounders were ascertained from nationwide health registries.

MAIN OUTCOME MEASURES Prevalence odds ratios (PORs) of any major birth defect diagnosed within the first year of life by fetal exposure to antiepileptic drugs.

RESULTS Of the 1532 infants exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam during the first trimester, 49 were diagnosed with a major birth defect compared with 19 911 of the 836 263 who were not exposed to an antiepileptic drug (3.2% vs 2.4%, respectively; adjusted POR [APOR], 0.99; 95% confidence interval [CI], 0.72-1.36). A major birth defect was diagnosed in 38 of 1019 infants (3.7%) exposed to lamotrigine during the first trimester (APOR, 1.18; 95% CI, 0.83-1.68), in 11 of 393 infants (2.8%) exposed to oxcarbazepine (APOR, 0.86; 95% CI, 0.46-1.59), and in 5 of 108 infants (4.6%) exposed to topiramate (APOR, 1.44; 95% CI, 0.58-3.58). Gabapentin (n = 59) and levetiracetam (n = 58) exposure during the first trimester was uncommon, with only 1 (1.7%) and 0 infants diagnosed with birth defects, respectively.

CONCLUSION Among live-born infants in Denmark, first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam compared with no exposure was not associated with an increased risk of major birth defects.

F.D.A REPORT ON TOPIMARATE

ISSUE: FDA notified healthcare professionals and patients of an increased risk of development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with Topamax (topiramate) during pregnancy. Because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D. Pregnancy Category D means there is positive evidence of human fetal risk

based on human data but the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks. The patient medication guide and prescribing information for Topamax and generic topiramate will be updated with the new information.

BACKGROUND: Topiramate is an anticonvulsant medication approved for use alone or with other medications to treat patients with epilepsy who have certain types of seizures. Topiramate is also approved for use to prevent migraine headaches. The new data was from the North American Antiepileptic Drug (NAAED) Pregnancy Registry

RECOMMENDATION: Before starting topiramate, pregnant women and women of childbearing potential should discuss other treatment options with their health care professional. Women taking topiramate should tell their health care professional immediately if they are planning to or become pregnant. Patients taking topiramate should not stop taking it unless told to do so by their health care professional. Women who become pregnant while taking topiramate should talk to their health care professional about registering with the North American Antiepileptic Drug Pregnancy Registry, a group that collects information about outcomes in infants born to women treated with antiepileptic drugs during pregnancy.

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http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm245777.htm

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S-ADENOSYL METHIONINE (SAME) AUGMENTATION OF SEROTONIN REUPTAKE INHIBITORS FOR ANTIDEPRESSANT NONRESPONDERS WITH MAJOR DEPRESSIVE DISORDER: A DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL

Papakostas GI et al - Am J Psychiatry 2010 Aug

Over the years, a modest literature has suggested that S-adenosyl-methionine (SAMe) may have moderately effective antidepressant properties. This molecule, a methyl donor to many neurotransmitters, is available in over-the-counter preparations. Researchers now report the first-ever, randomized, controlled trial of SAMe's efficacy and tolerability as an adjunctive treatment for patients with major depressive disorder that is not responding to treatment with serotonin reuptake inhibitors (SRIs).

In the National Institute of Mental Health-funded, 6-week, single-site trial, 73 patients received either SAMe (target dose, 800 mg twice daily) or placebo added to their prior stable medication (most commonly, escitalopram, duloxetine, and fluoxetine). Intent-to-treat analyses showed significantly higher response and remission rates with SAMe than with placebo (response: 46.1% vs. 17.6%; remission: 35.8% vs. 11.7%; data as confirmed in personal communication with study author). No differences were found in rates of dropouts or adverse effects. No instances of serotonin syndrome were observed with the SAMe and SRI combination.

Comment: The findings in this pilot study are comparable to those found with various augmenting agents in the STAR*D trials. Whether SAMe proves to be equivalent to other augmenting agents across a wide range of patient characteristics or shows specificity for certain types of treatment-resistant depression remains to be assessed in better-powered and longer trials. How cost-effective is SAMe relative to other augmenting agents? The answer may depend on your patients' insurance plans, the availability of discounts for generic medications in your area, and the going rate for SAMe at your local supermarket or big box store.

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http://psychiatry.jwatch.Org/cgi/content/full/2010/823/2

SUICIDE-RELATED EVENTS IN PATIENTS TREATED WITH ANTIEPILEPTIC DRUGS

Arana A et al _ N Engl J Med 2010

In an FDA meta-analysis of randomized, controlled, clinical trials of antiepileptic drugs, AEDs were associated with suicidality. Now, researchers in a manufacturer-funded study have used data on 5,130,795 patients seen in U.K. primary care clinics to examine the role of the underlying diagnosis in this association. Patients with personal or family histories of suicide were excluded. The diagnostic cohorts were epilepsy, bipolar disorder, depression, and none of these three; analyses were restricted to suicide attempts or completions.

As expected, rates of these events were significantly higher in patients with depression or bipolar disorder and slightly higher in patients with epilepsy compared with patients without these diagnoses and without AED use. In a case-control analysis adjusted for multiple confounders, no association was found between AED use and suicide-related events in the epilepsy or bipolar disorder cohorts. However, in patients with depression only, risk for these events increased with AED use, but this increase was much smaller than the effect of having depression. AED users with none of these conditions also had significantly increased risk for suicide-related events.

Comment: In general, these results do not corroborate the FDA's finding of a relation between antiepileptic drugs and suicide, except in depressed patients, for whom AEDs may be less specifically therapeutic, and in patients with none of the examined illnesses, who might take AEDs for pain or other conditions that increase suicide risk. Some confounding by indication probably persisted (i.e., depressed patients receiving AEDs may have been sicker or more treatment-refractory and hence at higher risk for suicide). However, the study's many strengths include study of a patient population without suicide histories who were seen in primary care clinics; focus on suicide attempts and completions and not on ideation; and, most important, stratification of the analyses by illness. This finding suggests that the illness is more important than the medication in increasing the risk for suicide.

http://psychiatry.jwatch.org/cgi/content/full/2010/804/1

EPIGENETIC TRANSMISSION OF THE IMPACT OF EARLY STRESS ACROSS GENERATIONS

Franklin TB et al - Biol Psychiatry 2010

Genetic factors influence psychological states, but could the reverse be true? Recent study results in rodents and humans suggest that early experience can alter gene expression.

Franklin and colleagues carefully designed an animal study to eliminate the direct environmental impact of early experience and maternal factors on later generations. First, infant mice (F1 generation) were exposed to 3 hours daily of unpredictable separation from mothers undergoing random maternal stress. Weaned F1 males were mated with nonstressed females and then separated from the pregnant females. Their normally raised male offspring (F2) were bred with other nonstressed females to create F3 offspring. In behavioral testing, anhedonia-like behavior (a possible animal proxy for depression) was not transmitted through the generations, but depression-like behaviors and abnormal stress response were inherited. Compared with normally reared controls, F1 males and F2 females exhibited greater depression-like behavior, which was reversed by the antidepressant desipramine. F3 males, but not F2 males, exhibited depression-like behaviors. Compared with controls, only F1 males had more anhedonia-like behavior. F1 males, F2 females, and F3 females exhibited abnormal stress responses. The sperm of F1 males showed low methylation of the promoter for a corticotrophin-releasing factor gene and high methylation of the promoter of a cannabinoid receptor gene (involved in rodent emotional regulation) and of a gene coding for a transcriptional regulator. The brains of F2 females showed similar methylation changes.

In a reanalysis of data on 143 people, van IJzendoorn and colleagues assessed genotype and methylation status of the serotonin transporter promoter (5-HTTLPR) and questionnaire responses on unresolved feelings about early loss or trauma. Genotype (two short alleles, two long alleles, or heterozygote) had no main effect on unresolved feelings. However, in individuals with two short alleles (usually associated with lower gene expression), degree of methylation significantly predicted unresolved feelings - fewer with higher methylation and greater with lower methylation.

Comment: Epigenetics is the process by which experience alters gene expression. One epigenetic mechanism is DNA methylation, which usually silences genes but sometimes turns them on. Franklin and colleagues' study results indicate that a stressful upbringing alters methylation of multiple genes and that this alteration

is passed to subsequent generations, even without relevant early experiences, in a complicated, sex-linked dynamic that modifies the stress response. The results of the study by van IJzendoorn and colleagues might suggest that methylation status of a particular gene predisposes to unresolved loss rather than results from it. That the lower activity level of short-allele individuals experiencing early trauma or loss seems to improve resilience contradicts other research. Not all molecular biologists agree that DNA methylation explains the influence of early experience on biology, and there are undoubtedly additional important mechanisms yet to be identified. At the least, the study demonstrates that altered DNA methylation occurs in people. Clinicians should consider early adverse experience in one generation as a risk factor for psychopathology in later generations.

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http://psychiatry.jwatch.org/cgi/content/full/2010/1018/1?q=topstorieslanding

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PATTERNS OF NONADHERENCE TO ANTIEPILEPTIC DRUG THERAPY IN CHILDREN WITH NEWLY DIAGNOSED EPILEPSY

Modi AC et al - JAMA 2011 Apr 27

Investigators prospectively examined the pattern and determinants of antiepileptic medication adherence in 124 consecutive children (age range, 2-12 years) with newly diagnosed seizures. Adherence during the first 6 months of therapy (carbamazine or valproic acid twice daily) was measured using an electronic medication monitoring system.

The authors identified five patterns of adherence. Severe early nonadherence described the 13% of children who took 25%-50% of prescribed doses during the first month and become totally nonadherent within 6 months. Severe delayed nonadherence described the 7% of children whose high adherence declined over time to only 20% of doses at 6 months. Moderate nonadherence described the 13% of children who averaged 70% of medications. Mild nonadherence referred to children who averaged 85% of doses. Only 42% of children had near-perfect adherence. The only variable that predicted adherence trajectory was socioeconomic status (SES); lower SES was associated with poorer adherence. Seizure type and severity, frequency of adverse events, and whether a parent witnessed the first seizure did not predict adherence.

Comment: Nearly 60% of children with newly diagnosed seizures do not adhere to their seizure medication dosing schedule during the first 6 months of therapy. Unfortunately, the only predictor of adherence - SES - is beyond the therapeutic power of providers, but it can help identify children at risk for nonadherence. Providers can suggest ways to improve adherence to dosing schedules (e.g., use of calendars or alarms). Visiting nurses might be considered to periodically monitor medication compliance for some patients.

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http://pediatrics.jwatch.org/cgi/content/full/2011/518/1

ZOLPIDEM AND ZOPICLONE IMPAIR SIMILARLY MONOTONOUS DRIVING PERFORMANCE AFTER A SINGLE NIGHTTIME INTAKE IN AGED SUBJECTS

A single dose may Impair driving the next morning in people older than 55.

Bocca M.L.et al - Psychopharmacology

Zolpidem has been shown to lack residual effects on driving the next day in young and middle-aged recipients. However, information is sparse on its effects on driving in older individuals, even though use of hypnotic's increases with age. In a double-blind, crossover study, researchers examined how a single nighttime dose of zolpidem, another hypnotic, or benzodiazepine affected driving the next morning in 16 healthy subjects (8 women) aged 55 to 65 years.

Subjects lacked sleep disorders, histories of substance abuse, or impaired vision. On separate occasions at least 2 weeks apart, the subjects took zolpidem 10 mg, the hypnotic zopiclone 7.5 mg, the benzodiazepine flunitrazepam 1 mg, or placebo at night. The next day, they were tested in a driving simulator in urban and monotonous driving conditions.

All subjects slept during the experimental nights, as verified by polysomnography. Compared with placebo, zolpidem was associated with next-day significantly greater difficulty in keeping the car in the lane and maintaining a constant speed. Impairment was similar after zopiclone, but was less with flunitrazepam, which the investigators attributed to the low dosage. The morning after taking zolpidem, subjects reported lower alertness; 11 had detectable zolpidem blood levels.

COMMENT: In this small study, researchers did not compare driving performance in people of different ages and examined effects of only acute, not regular, medication use. Despite these limitations, the results raise concerns about possible impairment in routine, monotonous driving in individuals in their 50s or 60s starting on zolpidem or taking it as needed. Fortunately, subjects were aware of their diminished alertness. Clinicians should consider prescribing a lower starting dose of zolpidem (5 mg) even in patients younger than 65 and should warn patients against driving if they feel sedated.

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http://www.ncbi.nlm.nih.gov/pubmed/21086117? dopt=Abstract]

NORADRENERGIC ENHANCEMENT OF RECONSOLIDATION IN THE AMYGDALA IMPAIRS EXTINCTION OF CONDITIONED FEAR IN RATS - A POSSIBLE MECHANISM FOR THE PERSISTENCE OF TRAUMATIC MEMORIES IN PTSD

D biec J et al - Depress Anxiety 2011 Mar

Norepinephrine is involved in memory consolidation and fear learning. These investigators used a rat model of fear conditioning (tone/footshock) to examine how norepinephrine affects the maintenance and exacerbation of fear memories.

One day after fear conditioning, rats received infusions, into the lateral nucleus of the amygdala, of the beta-adrenergic agonist isoproterenol or saline, either after reactivation of fear memories or without memory reactivation. Two days later, rats underwent memory extinction. In rats given isoproterenol plus memory reactivation, freezing (fear response) to the conditioned tone was enhanced, and fear memories became more resistant to extinction. Memory reactivation alone, or isoproterenol alone, did not affect fear extinction.

In another experiment, fear-conditioned rats underwent two memory reactivations, each of which was followed by infusions of isoproterenol, the beta-adrenergic antagonist propranolol, or saline. After the second reactivation, the fear response was lower in rats first given propranolol and then saline and greater in rats given isoproterenol and then saline, compared with rats given saline twice. Extinction was impaired in rats given isoproterenol + saline compared with rats given saline twice, was enhanced in rats given propranolol + saline, and was at an intermediate level in rats given isoproterenol and propranolol in any order.

Comment: Infusing isoproterenol into the lateral amygdala of rats after retrieval of conditioned fear impairs fear extinction 48 hours later. In humans, noradrenergic activity during trauma enhances traumatic memories, and propranolol after trauma decreases the risk for post-traumatic stress disorder. These results suggest that levels of noradrenergic activity and arousal during later retrieval of traumatic memories may also affect the course, severity, and persistence of PTSD. Studies of adrenergic antagonists plus exposure therapy as a PTSD treatment would be valuable.

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http://psychiatry.jwatch.org/cgi/content/full/2011/425/4?q=etoc_jwpsych

ANTIDEPRESSANT EFFECTS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) ARE ATTENUATED BY ANTIINFLAMMATORY DRUGS IN MICE AND HUMANS

Warner-Schmidt JL et al. Proc Natl Acad Sci U S A 2011 Apr

Cytokines may be important in depression. These immunomodulators are produced by glial cells, regulate brain serotonin and noradrenergic systems, and activate the hypothalamic-pituitary-adrenal axis. Antidepressants increase levels of p11, a specific protein that regulates depression in rodent models and interacts with the serotonin receptor. To learn about possible interactions of antidepressants, cytokines, p11, and anti-inflammatory drugs (NSAIDs), researchers conducted experiments in mice and reanalyzed data from the large STAR*D study.

The selective serotonin reuptake inhibitors citalopram and fluoxetine increased p11 levels in mouse frontal cortex, but coadministered ibuprofen (IBU) or acetylsalicylic acid (ASA) blocked this increase. IBU lowered plasma citalopram levels. The tricyclic desipramine produced a small p11 increase, which was not affected by IBU or ASA. Antidepressant-related p11 increases were dependent on signaling by two cytokines (interferon-gamma and tumor necrosis factor-alpha). In a mouse model of depression, IBU, ASA, and acetaminophen prevented the behavioral response to SSRIs but not to antidepressants of other types.

Of STAR*D patients who took citalopram for 12 weeks, significantly fewer achieved remission if taking NSAIDs than if not taking NSAIDs (45% vs. 55%). Findings were similar in a comparison of other analgesic use with nonuse (37% vs. 54%).

Comment: This elegant translational study connects the observations in a rodent depression model with possible clinical response to antidepressants. SSRIs (but not noradrenergic antidepressants) increase cytokines, which increase p11, resulting in the antidepressant response. NSAIDs (and acetaminophen) inhibit the step-activating cytokines. Clinically, worse antidepressant response is associated with analgesic use. Further research is needed, including prospective studies of various antidepressant types and studies of other possible etiologies - e.g., putatively NSAID-lowered plasma levels of SSRIs or a greater likelihood that depression will be refractory to treatment in patients with pain. Meanwhile, clinicians should carefully evaluate their depressed patients' analgesic use; it may be one reason for poor response. For patients requiring analgesics, clinicians may wish to consider non-SSRIs.

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http://psychiatry.jwatch.org
/cgi/content/full/2011/502/1

CLINICAL FEATURES AND APOE GENOTYPE OF PATHOLOGICALLY PROVEN EARLY-ONSET ALZHEIMER DISEASE

M. Balasa, MD and Colleagues

ABSTRACT

OBJECTIVES: Early-onset Alzheimer disease (EOAD) diagnosis often represents a challenge because of the high frequency of atypical presentations. Our aim was to describe the clinical features, APOE genotype, and its pathologic correlations of neuropathologic confirmed EOAD.

METHODS: Retrospective review of clinical data (age at onset, family history, clinical presentation, diagnostic delay, diagnosis) and APOE genotype of patients with neuropathologically confirmed EOAD (<60 years).

RESULTS: Forty cases were selected. Mean age at onset was 54.5 years (range 46-60). The mean disease duration was 11 years with a mean diagnostic delay of 3.1 years. A total of 37.5% had a nonmemory presentation. Behavioral/executive dysfunction was the most prevalent atypical presentation. Incorrect initial clinical diagnoses were common (53%) in patients with atypical presentations, but rare when anterograde amnesia was the presenting symptom (4%). The incorrect initial clinical diagnoses were 2 behavioral variant frontotemporal lobar degeneration, 2 normal pressure hydrocephalus, 1 semantic dementia, 1 primary progressive aphasia, 1 corticobasal degeneration, 1 pseudodementia with depression, and 1 unclassifiable dementia. APOE genotype was ?3/?3 in 59%, with no significant differences between typical and atypical presentations. APOE ?4 was 3.3 times more frequent in subjects with family history of AD. A total of 97.5% of the cases presented advanced neurofibrillary pathology. A total of 45% of the patients had concomitant Lewy body pathology although localized in most cases and without a significant clinical correlate.

CONCLUSION: One third of patients with pathologic confirmed EOAD presented with atypical symptoms. Patients with EOAD with nonamnestic presentations often receive incorrect clinical diagnoses.

http://neurology.org/content/76/20/1720.abstract

REMISSION PROGNOSIS FOR COGNITIVE THERAPY FOR RECURRENT DEPRESSION USING THE PUPIL: UTILITY AND NEURAL CORRELATES

Siegle GJ et al. Biol Psychiatry 2011 Apr 15; 69:726.

Cognitive therapy (CT) is clearly effective for mild-to-moderate depression but less so for more-severe depression. These authors investigated whether pupillary response to negatively charged words could predict CT-related remission in more severely depressed patients.

The researchers assessed pretreatment depression severity in 32 outpatients with recurrent major depression and 51 nondepressed controls. Assessment of pupillary dilation was conducted while participants identified words as positive, negative, or neutral; 20 participants also underwent functional magnetic resonance imaging (fMRI) during pupil dilation. Measurements were repeated after 16 to 20 CT sessions.

Six of seven patients with an initial Beck Depression Inventory (BDI) score 20 remitted (defined as BDI score <10 and no criteria for major depressive disorder); among 25 patients with an initial BDI score >20, 11 remitted. In the latter group, pupil dilation in response to negative words was greater in nonremitters and lesser in remitters (82% sensitivity, 93% specificity). Pupil dilation in remitters was associated with increased activity in the left dorsolateral prefrontal cortex (DLPFC) on fMRI.

Comment: The authors hypothesize that pupil dilation in response to negative words associated with DLPFC activation represents mobilization of executive control over emotional arousal. Because CT enhances executive control, less pretreatment pupil dilation might identify those with less executive control of affect and, therefore, those more likely to benefit from CT, whereas those with greater pupillary dilation and presumably better executive function may not gain as much benefit from this technique. The practical implication is that while any less severely depressed patient has a good chance of benefiting from CT, evaluation of pupil dilation in response to negative words might identify which more severely depressed patients should consider CT. As the equipment used in this study costs $12,000, and the software is available without charge from the principal investigator, the benefit may be worth the cost.

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http://psychiatry.jwatch.org/cgi/content/full/2011/516/2

COMBINING MEDICATIONS TO ENHANCE DEPRESSION OUTCOMES (CO-MED): ACUTE AND LONG-TERM OUTCOMES OF A SINGLE-BLIND RANDOMIZED STUDY

Rush AJ et al. Am J Psychiatry 2011 May 2

Clinicians are sometimes tempted to initiate, or switch to, treatment with two antidepressants in patients with chronic or recurrent major depression episodes. To assess the merit of this strategy, researchers in a National Institute of Mental Health-funded, multisite, placebo-controlled, 7-month study randomized 665 patients with chronic or recurrent depression to one of three treatments:

- Escitalopram (10-20 mg/day) plus placebo (monotherapy)
- Sustained-release bupropion (150-400 mg/day) plus escitalopram
- Extended-release venlafaxine (37.5-300 mg/day) plus mirtazapine (15-45 mg/day)

Clinicians could vary doses according to patient response at scheduled intervals. Some study exclusions were lack of response to an FDA-approved monotherapy in the current episode or, in chronic depression, during the previous 2 years; lack of response to adequate trials of any study medication or combination; or use of a study medication at study entry.

Patients were moderately to severely ill, 75% had concurrent anxiety, and comorbid Axis I and Axis III disorders were common. After 12 weeks, no group differences were seen in rates of remission (37.7%-38.9%) or response (51.6%-52.4%). More adverse effects were seen in the venlafaxine+mirtazapine combination group than in other groups. After 7 months, results were essentially unchanged, with modest increases in remission (41.8%-46.6%) and response (57.4%-59.4%).

Comment: The study had several limitations: There was no pure placebo group, comorbidities were not specifically addressed by the treatments, and dosages in some combinations were insufficient. Clearly, however, the combinations used in this study show no advantage over escitalopram alone for first-step treatment of the depressive mood component of these patients.

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THE NEURONAL TRANSPORTER GENE SLC6A15 CONFERS RISK TO MAJOR DEPRESSION

Kohli MA et al-Neuron 2011 Apr 28

Genome-wide association studies (GWASs) of candidate genes in depression have had limited success, with some studies not replicating previous findings and others failing to identify susceptibility genes. These researchers performed GWASs, cell and imaging studies, and animal studies.

First, the researchers identified a candidate gene, which codes for a transporter of large amino acids in the central nervous system, in a case-control GWAS and replicated the finding in six independent samples (total of 4088 patients and 11,001 healthy controls). The investigators subsequently explored "intermediate phenotypes" previously linked with depression pathophysiology. Among their findings:

- The gene was shown to control expression of the relevant messenger RNA in human hippocampal tissue.
- Carriers of either of the two identified risk single-nucleotide polymorphisms (SNPs) had reduced mRNA expression in blood monocytes.
- In magnetic resonance imaging of 390 depressed and healthy SNP carriers and noncarriers, depressed carriers had the lowest hippocampal gray matter volume.
- In 81 healthy controls, SNP carriers had lower hippocampal N-acetyl aspartate and glutamate levels on spectroscopy than noncarriers.
- The gene had lower expression in hippocampi of stress-sensitive mice than in stress-resilient mice.

Comment: In this impressive study series, researchers identified and replicated an amino-acid transporter gene variant linked with depressive illness in multiple patient samples, showed the gene's relevance to stress sensitivity in animals, and found specific associations with human hippocampal atrophy and loss of hippocampal neuronal integrity theorized to underlie depression pathophysiology. This pathophysiology has been linked to glutamate neurotransmission (a current focus of new approaches to depression treatment); a precursor of glutamate synthesis is a substrate for the transporter coded for by this gene. These studies could inform the development of new treatments for depression and further elucidate the pathophysiology of this common and often disabling illness.

http://psychiatry.jwatch.org/cgi/content/full/2011/523/1

ANTIEPILEPTIC DRUGS INTERACT WITH FOLATE AND VITAMIN B12 SERUM LEVELS

Linnebank M et al - Ann Neurol 2011 Feb

Studies of a potential association between use of antiepileptic drugs (AEDs) and reduced serum levels of folate and vitamin B12 have yielded conflicting results. To elucidate the issue, researchers prospectively studied 2900 patients with epilepsy (2730 treated with AEDs, 170 untreated) seen at one center in Germany (where food is not routinely supplemented with folate) and 200 healthy controls.

Subnormal serum folate levels were significantly more common in AED recipients than in either untreated epilepsy patients or healthy controls. This finding held for carbamazepine, gabapentin, phenytoin, primidone, oxcarbazepine, and valproate; in the context of AED monotherapy, the finding held for all drugs in this list except oxcarbazepine and valproate. Dose-dependent associations between drug use and folate reduction were found for carbamazepine, primidone, and valproate.

Associations between AED use and reduced serum vitamin B12 levels were also found, but for fewer drugs and to a lesser extent. Only pregabalin and topiramate had significant dose-dependent associations with modestly reduced (not subnormal) vitamin B12 levels. AED monotherapy (with any drug) was not associated with reduced B12 levels; in fact, valproate monotherapy was associated with increased B12 levels.

Comment: This is the most exhaustive, definitive study to date regarding the association of AEDs with reduced serum levels of folate and vitamin B12. With respect to folate in particular, the data strongly confirm the association for many individual AEDs as well as for all functional categories of AED (metabolic-enzyme inducers, noninducers, and inhibitors). Although inducers such as phenytoin and carbamazepine had the clearest associations, enzyme induction cannot be more than a contributing factor, leaving the main cause or causes a mystery. The authors discuss several causal possibilities, including AED interference with diet, vitamin absorption, plasma binding, metabolism, and excretion. The lack of association between use of AEDs such as levetiracetam and benzodiazepines and reductions in folate and B12 levels just adds to the confusion.

The authors discuss the potential clinical significance of their findings in relation to hyperhomocysteinemia and the metabolic consequences of insufficient folate and vitamin B12. However, the clinical significance of these data is uncertain, as folate supplementation of certain foods is mandatory in many countries. Furthermore, this study was not designed to assess whether modestly subnormal levels of folate and B12 significantly affect clinical symptoms. Nevertheless, these intriguing findings should prompt greater interest in the metabolic consequences of chronic AED use.

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CAN SEMIOLOGY PREDICT PSYCHOGENIC NONEPILEPTIC SEIZURES? A PROSPECTIVE STUDY

Syed TU et al - Ann Neurol 2011 Mar 17

Among the most underappreciated costs and patient burdens in seizure disorders are those of misdiagnosis of epileptic seizures (ES) and delayed diagnosis of psychogenic nonepileptic seizures (PNES). To see whether clinical history could facilitate diagnosis, researchers sought to determine which seizure signs distinguish between ES and PNES and whether eyewitnesses accurately identify those signs.

Thirty-five adults were consecutively enrolled at an epilepsy monitoring unit. These patients, who experienced 120 video-documented seizures (36 PNES, 84 ES) seen by eyewitnesses, were referred for inpatient evaluation with video electroencephalography (VEEG). Epileptologists, blinded to diagnosis information and EEG tracings, assessed the video recordings of the seizures for the presence or absence of 48 prespecified semiological signs (roughly equally divided between PNES and ES signs). Associations between epileptologists' identifications of signs and VEEG-determined diagnoses were assessed in the original 35-patient cohort and in a validation cohort of 36 patients. Statistically significant associations were found for six signs: three for PNES ("preserved awareness," "eye flutter," and "others [bystanders] can intensify or alleviate [the seizure]") and three for ES ("eye opening or widening at onset," "abrupt onset," and "[postseizure] confusion/sleep"). However, eyewitnesses' reports of these six signs were not accurate and, therefore, not significantly associated with VEEG-determined diagnoses.

Comment: The findings of this well-designed prospective study confirm the difficult clinical challenge of diagnosing PNES accurately. Remarkably, it is not uncommon for patients with PNES to be diagnosed with and treated for epilepsy for years (although not nearly the "average" of 7 to 10 years that the authors assert). The authors call for better education of seizure patients' family members in how to identify the most diagnostically useful and reliable signs. That proposal is reasonable, but more obvious is the need to educate healthcare providers and insurers that prompt VEEG monitoring is indicated in all patients with uncontrolled seizures, regardless of what seizure type is suspected.

http://neurology.jwatch.org/cgi/content/full/2011/524/1?q

AAV2-GAD GENE THERAPY FOR ADVANCED PARKINSON'S DISEASE: A DOUBLE-BLIND, SHAM-SURGERY CONTROLLED, RANDOMISED TRIAL

LeWitt PA et al - Lancet Neurol 2011 Apr; 10

The standard of care for surgically treating patients with Parkinson disease (PD) is deep brain stimulation (DBS), wherein electrical stimulation of the subthalamic nucleus (STN) diminishes its output, thus freeing the ventrolateral thalamus and associated thalamocortical motor circuitry from the STN's indirect modulatory influence. However, DBS does not improve all PD symptoms. In an industry-supported, double-blind, randomized trial of gene therapy for PD, researchers used a viral vector to insert the gene for glutamic acid decarboxylase (GAD) into the STN. GAD is the rate-limiting enzyme in the synthesis of -aminobutyric acid (GABA), the neurotransmitter in afferent STN terminals. Augmenting GABAergic transmission attenuates the output of the STN, producing an effect analogous to that of DBS.

Outcomes of GAD gene infusion and sham surgery were analyzed in 16 and 21 patients, respectively. At 6 months, motor scores improved from baseline by 23.1% in the GAD group and 12.7% in the sham group (a statistically significant between-group difference of 10.4%).

Comment: The meticulous design of this study enabled the investigators to detect a somewhat modest improvement as a significant effect, all of which points to the importance of fastidiousness in small surgical trials. By comparison, a similarly sized, placebo-controlled study of intraputamenal infusion of glial-derived neurotrophic factor (GDNF; Ann Neurol 2006; 59:459) was carried out less carefully; because it could not rule out a between-group difference of 23%, the latter study should have been reported as inconclusive - rather than negative - and the trial should have been repeated with a more scrupulous design (J Neurosci Methods 2007; 163:190).

The current study is the first demonstration that gene therapy shows promise as a treatment for PD. The intervention is not curative; furthermore, the effect size is smaller than that achieved with DBS. Unless future trials reveal bigger improvements, gene therapy is unlikely to replace standard surgical treatment. However, the results suggest that gene therapy can yield lasting relief for patients with PD, and this trial might therefore pave the way to more-definitive genetic manipulations, such as inserting the GDNF gene into the putamen.

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http://neurology.jwatch.org/cgi/content/full/2011/524/2?q

CLINICAL AND PSYCHOSOCIAL PREDICTORS OF SUICIDE ATTEMPTS AND NONSUICIDAL SELF-INJURY IN THE ADOLESCENT DEPRESSION, ANTIDEPRESSANTS AND PSYCHOTHERAPY TRIAL (ADAPT)

Wilkinson P et al.. Am J Psychiatry 2011 Feb

To investigate possible connections among depression, self-injury, and suicide attempt in teenagers, researchers comprehensively interviewed 164 adolescents with major depression enrolled in a treatment study of cognitive-behavioral therapy added to selective serotonin reuptake inhibitors and specialist care. Participants were asked about nonsuicidal self-injury in the month before baseline (prebaseline) and after 28 weeks of treatment and about previous-month depressive symptoms, including suicidal ideation, at 6, 12, and 28 weeks.

Independent predictors of suicide attempts at 28 weeks included high suicidal ideation ratings, prebaseline nonsuicidal self-injury, and impaired family functioning. Predictors of nonsuicidal injury during treatment were prebaseline nonsuicidal injury, female sex, being younger, and baseline hopelessness and anxiety disorder. Incidence of suicide attempts during treatment was tenfold higher in patients with prebaseline nonsuicidal injury than in those with good family functioning and no self-injury. Suicide attempts and nonsuicidal self-injury were less frequent during treatment than at prebaseline. Nonsuicidal self-injury was associated with high depressive symptoms at week 28.

Comment: Several study limitations include lack of data on known predictors of suicide attempts, including substance use disorders and family history of suicide. Also, the secondary analyses in this study can produce unwarranted results, and thus the study needs replication. Nevertheless, these findings inform clinicians that self-injurious behaviors may increase risk for suicide attempt, even in patients undergoing depression treatment. The psychosocial results accord with those from other studies, providing further support for the need to address family functioning in adolescents who have attempted suicide.

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http://psychiatry.jwatch.org/cgi/content/full/2011/228/3

PREVENTING THE RETURN OF FEAR IN HUMANS USING RECONSOLIDATION UPDATE MECHANISMS

Schiller D et al - Nature 2010

When animals recall a fear memory, it is reconsolidated with new material. In rats, inhibitors of protein synthesis in the amygdala prevent reconsolidation of fear memories, permanently erasing them. Thus, these drugs are not viable for humans seeking relief from post-traumatic stress or anxiety disorders. Other researchers have found that fear extinction persists when a reminder (cue plus shock) precedes extinction training by less than 6 hours. The researchers in the current study examined nondrug methods to modify fear memories during reconsolidation in humans.

Volunteers (N=65) received mild electric shocks while viewing a colored square. Fear was assessed using skin conductance response, which relies on sweat production. Extinction training (viewing the square without being shocked) occurred 24 hours later. Two groups of volunteers had received a reminder, which occurred 10 minutes before extinction training in group 1 and more than 6 hours beforehand in group 2; group 3 received no reminder. All groups achieved fear extinction. On day 3, researchers found fear responses in groups 2 and 3 but none in group 1. One year later, 23 volunteers were retested; lack of fear response persisted in group 1 volunteers, unlike the others.

To test specificity of this response, the researchers conducted another experiment that additionally used another colored square, for which no reminder was given before extinction training. Fear responses to squares with reminder shocks were extinguished in the 18 volunteers.

Comment: These elegant studies provoke many questions. For example, would this method work for traumas more complex than colored squares and mild shocks? Would extinguishing fear related to a traumatic battlefield memory also extinguish appropriate responses to scenarios involving firearms? Would the method be effective if extinction training occurred years, rather than 24 hours, after a traumatic situation?

http://psychiatry.jwatch.org/cgi/content/full/2010/113/4?

DAILY LEFT PREFRONTAL TRANSCRANIAL MAGNETIC STIMULATION THERAPY FOR MAJOR DEPRESSIVE DISORDER: A SHAM-CONTROLLED RANDOMIZED TRIAL

George MS et al- Arch Gen Psychiatry 2010

Research into the efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression has produced variable results and prompted questions about the adequacy of the sham control. In this NIH-sponsored study, researchers randomized 190 antidepressant-free patients with unipolar nonpsychotic major depression to sham or active, moderately fast, left prefrontal rTMS (10 Hz). Patients had failed an average of 1.5 antidepressant trials for the current episode and 3.3 antidepressant trials in their lifetimes.

Patients were treated weekdays (37.5 minutes/session) for 3 weeks. Then, remitters began antidepressant medication, improvers (30% improvement in Hamilton Rating Scale for Depression [HRSD] score) continued their assigned treatments until they remitted or stopped improving, and nonimprovers began open-label rTMS (phase 2). The primary outcome measure was remission (HRSD score, 3 or 2 consecutive scores <10) at 3 weeks, which occurred in six patients (14%) receiving active treatment and in two (5%) receiving sham treatment. In phase 2, 30% of patients remitted with active treatment.

Comment: Although rTMS was significantly more likely than sham treatment to produce remission, the number of remitters was unimpressive. Although the mean change in scores at 3 weeks on one scale (rTMS, 17%; sham, 7%) was statistically significant, the mean score in both groups remained at a similar level of severity. It is encouraging that almost one third of patients were in remission after phase 2, but this was a secondary outcome, with many patients not completing the entire treatment course. The most conservative conclusion is that left prefrontal rTMS may be an effective acute treatment for patients without complex mood disorders resistant to antidepressants. As yet, no evidence of effectiveness exists for rTMS in severe, psychotic, bipolar, or refractory depression, although effectiveness in these conditions would better justify the treatment's expense. The best maintenance treatment after acute rTMS remains unknown.

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http://psychiatry.jwatch.org/cgi/content/full/2010/614/6

SHORT-TERM MEDITATION INDUCES WHITE MATTER CHANGES IN THE ANTERIOR CINGULATE

Tang Y-Y et al - Proc Natl Acad Sci U S A 2010

Researchers have found that a technique of short-term meditation (3 hours of training) decreases anxiety, depression, anger, and fatigue and improves efficiency in executive attention. The same group later showed that 11 hours of meditation training improves the basal immune system. Now, the researchers report the effects of 11 hours of integrative body-mind training (IBMT) on white-matter connectivity, as measured by fractional anisotropy (FA), which was calculated from diffusion tensor imaging. IBMT involves "body relaxation, mental imagery, and mindfulness training, accompanied by selected music background."

For 1 month, 45 undergraduate volunteers received 30 minutes, 5 days per week, of IBMT or, as a control, relaxation training. In the IBMT group, FA increased from baseline (indicating greater connectivity) in the left anterior corona radiata (ACR), the body and genu of the corpus callosum, bilateral superior corona radiata, and left superior longitudinal fasciculus. No changes were seen in measures of gray-matter volume.

Comment: The ACR connects the anterior cingulate cortex to the striatum, and increased connectivity of these regions has been related to improved executive attention. The FA increase in ACR may reflect either changes in white-matter organization or myelinization. The findings also might imply increased interhemispheric communication, reflected in changes in the corpus callosum. The clinical effects and possible therapeutic applications of IBMT are intriguing. Other recent study findings raise further questions about whether IBMT might modulate chronic stress and fear of social rejection. (The authors are currently developing a manual and CD for IBMT.)

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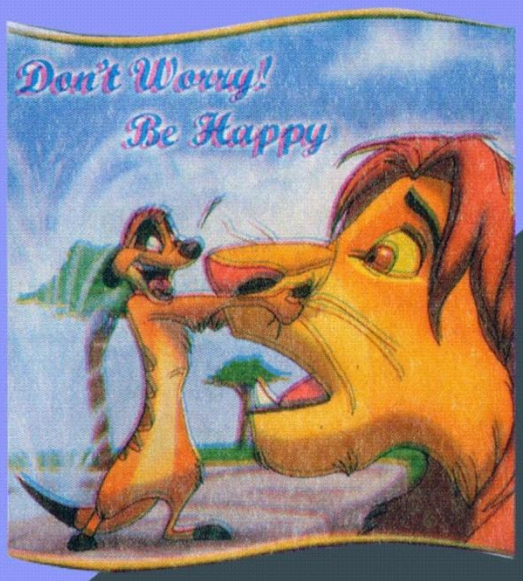

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