TREATMENT OF DISTURBED NIGHT SLEEP AND DAYTIME SLEEPINESS IN PARKINSON'S DISEASE

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Disturbances of sleep and wakefulness in Parkinson's disease (PD) are multifactorial in origin, and have manyfold clinical manifestations. The treatment approach should be as specific as possible (Högl B, Poewe W; 2003). In terms of sleep disorders, improving night time motor symptoms is the first step, whenever nocturnal akinesia tremor, or painful dystonia are present. Bed-time doses of long acting dopamine agonists may be helpful in this situation. In REM sleep behavior disorder, clonazepam is the treatment of choice, but a potential worsening of sleep apnea should be kept in mind. Obstructive sleep apnea syndrome may also be a main cause of disturbed sleep in PD and require nasal CPAP therapy. RLS and also severe PLMD, when increasing sleep fragmentation, require optimization of dopaminergic treatment, sometimes additional opioides are indicated. Nocturia as a cause of sleep fragmentation may be helped by drugs like oxybutinin or tolterodine in case of detrusor hyperreflexia or can sometimes be relieved by intranasal desmopressin. For symptomatic treatment of insomnia, benzodiazepine receptor agonists, or benzodiazepines may be additionally needed. In dealing with daytime sleepiness, an attempt to eliminate possible causes is madatory, e.g. by modification of dopaminergic therapy (e.g. dose reduction, dose splitting, or switch to another substance) or treatment of underlying sleep apnea. For symptomatic treatment, modafinil has been demonstrated to be beneficial (e.g., Högl et al, 2002). Methylphenidate has been suggested, but controlled studies are lacking, and a potential worsening of levodopa-induced dyskinesias must be taken into account. Other potential wake-enhancing substances, e.g. bupropion have been suggested, but studies have not been performed until now.

SLEEPINESS AND PARKINSON'S

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Excessive sleepiness associated with Parkinson's Disease (PD) affects 16% to 51% of patients and contributes to morbidity, cognitive impairment, and reduced quality of life. Etiology may include PD-related neurodegenerative abnormalities, comorbid sleep disorders, secondary sleep disturbances, and medication side effects. Thus, risk for excessive sleepiness in PD may be increased by demographic, disease-specific, and treatment-related factors. Patients with PD often fail to report chronic sleepiness, underestimate its severity, or describe it imprecisely. Initial management includes sleep hygiene education, treatment of underlying sleep pathology and other medical disorders, and re-evaluation of medication. When excessive sleepiness persists despite these measures, adjunctive treatment with the wake-promoting agent, such as modafinil, central nervous system (CNS) stimulants, or other medication may be considered. Excessive sleepiness associated with Parkinson's disease (PD) is common [Tandberg et al, 1999; Stocchi et al, 2000; Ondo et al, 2001; Gjerstad et al, 2002; Hobson et al, 2002; Tan et al, 2002] and adversely affects physical and cognitive functioning, social relationships, and quality of life (QoL). [Roth and Rohers, 1996; Ondo et al, 2001; Gjerstad et al, 2002; Hobson et al, 2002] Despite growing awareness that excessive sleepiness is an important clinical issue in PD, the problem remains underidentified, undertreated, and of uncertain etiology.

PREMORBID AND MORBID PERSONALITY IN PARKINSON' S DISEASE: CLINICAL FEATURES

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In James Parkinson' s original definition of patients with the disease bearing his name, he stated that beside the neurological symptoms, 'the senses and intellects being uninjured' (Parkinson, 1817). After the increased interest on Parkinson's disease mostly started in the L-Dopa area growing awareness to mental changes like depression and intellectual impairment came up, in the last years dementia, characteristic premorbid and morbid features of patients with Parkinson' s disease has received comparatively little attention. The psychoanalytical orientated psychiatrist in the first half of the last century followed the opinion that certain characteristic features and psychological factors might be important for the development of the disease, as depression, suppressing aggressive tendencies and problems to express emotions etc. (Sands, 1942). Furthermore Parkinson's patients were claimed for punctuality and cleanness with trends towards perfectionism, conservatism and rigid moral standards. Peculiar features of the premorbid personality of Parkinson's patients were described by Toedes and Lees (1985) and in a detailed form by Poewe et al. (1985, 1990) and Gerstenbrand and Karamat (1999). As main sign of a Parkinson' s personality inflexibility, moral rigidity and pedantic behaviour are registrated. In their studies the Innsbruck group used a special test program including interviews with patients and their relatives, personality inventory (Giessen-Test) Adult Intelligence Scale (Wechsler Test) and for assessment of premorbid characters, a semi-standarised biographical interview with patients and their relatives , last not least a blinded graphomotor examination was analysed using samples from years ago. The personality structure was found as obsessive/compulsive behaviour (anancasticity), Parkinson' s patients are pedantic, introverted, abrehensive, irresolute, undecided, wavering, hesitant, sceptical, full of tension and self reproaching. As a special feature Parkinson's patients are workaholics, teetotallers and mostly non-smokers with adhedonic traits. In the newer world history some political leaders are known to suffer of Parkinson's disease at least Generalissimo Franco, Mao Tse Tung, Brezhnev and Adolf Hitler. Because of many existing documents it was possible to study the premorbid and morbid personality of Hitler (Gerstenbrand and Karamat, 1999). All the previous announced traits could be documented in his personality, Hitler was a workalkoholic, he had difficulties in relationship with woman, he was an urgeon for ceremonial ritual procedures at political meetings and sport events, organising the 'Reichsparteitag' in the style of Richard Wagner' s operas, the Meistersinger of Nürnberg and Tannhäuser. A special characteristic of Hitler was the failure of social and moral values and laws, constructing pseudo-ethical norm. Hitler had the obsession to have been elected by fate to safe Germany and Europe. Similar features as in Hitler's personality can be found in other leading persons suffering of Parkinsonian disease. Studies with Parkinson's patients of different ethnical groups and religious communities show interest parallels. The knowledge of a special personality of Parkinson's patients the anancastic personality with pedantic traits can be helpful in the management of the treatment program. Using the three columns medicaments, physiotherapy and psychological guidance the knowledge of the special features in Parkinson personality can be helpful as basic strategy. Important for patients is the fact that Parkinson' s patient generally are not suffering of dementia and be bothered by depression.

TEST PSYCHOLOGICAL RESULTS IN PD

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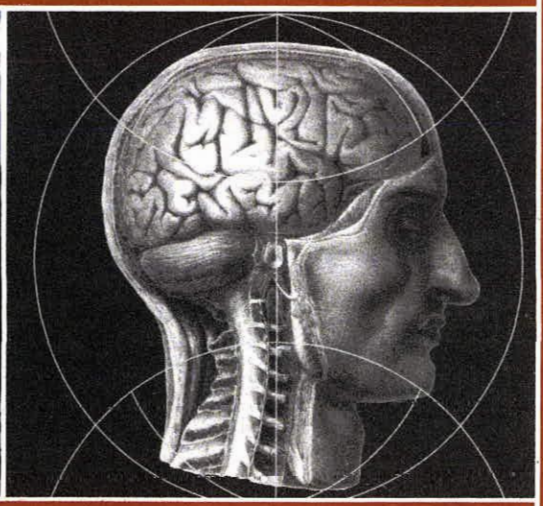
In this study the performance of 24 idiopathic PD patients and 24 elderly patients with lomboischialgic disease (LD), with MMSE scores falling within normal range i.e.Score<24, was compared on tests of cognitive capacities. The testbatterie referred to the following functions : Intelligence quotient (Raven), attention (digit span, ZVGT), verbal and visual short memory (wordlists and pictures of NAI), long term memory (Information of Hawie), visual and visuospational functions (picture completion and block design of Hawie), verbal functions (similarities) and executive functions (trail making test, lexical and semantic wordfluency, stroop-test) as well as mood factors (GDS of Yesavage). PD patients compared badly with LD participiants especially in executive function tasks showing increased mental rigidity. The two groups differed also in the performance of attentional and memory tasks. There was no significant difference regarding frequency und severity of depression.

MENTAL DYSFUNCTIONS IN PARKINSON'S DISEASE

SALZBURG, AUSTRIA
OCTOBER 24 - 27, 2004



FINAL PROGRAM & BOOK OF ABSTRACTS

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Tuesday, October 26, 2004

11:30 - 13:00 **Hall C**

PREMORBID AND MORBID PERSONALITY IN PD

Chairpersons: **F. Gerstenbrand**, Austria
E. Karamat, Austria

14:00 - 15:30 **Hall A**

COGNITIVE DYSFUNCTION IN PD: WHICH NEURO-TRANSMITTERS ARE RESPONSIBLE?

Chairpersons: **K.L. Leenders**, The Netherlands
T. van Laar, The Netherlands

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Premorbid and Morbid Personality in Parkinson's Disease Clinical Features

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LBI for Restorative Neurology, Vienna

Mental Dysfunctions in Parkinson's Disease
October 24-27, 2004
Salzburg,

Symptoms of Parkinson's Disease

30 % Loss of Dopamine 70

Preliminary sympt.	Early sympt.	Full stage
	Depression, fear	Rigidity
Memory dysfunction	Vegetative disorder	Tremor
Mood disorder	Vigilance	Akinesia
Performance brake	disturbance	Bradyphrenia
	Posture	Disturbance in
Sense of smell	abnormality	postural reflexes
dysfunction	hypokinesis	
	Pain in vertebral	Disturbance of
	Spine, headaches	cognitive
		performance
		Disturbance of
		autonomic NS

Parkinson, 1817, Shaking palsy:

"The senses and intellects being uninjured"

Growing awareness to mental changes like depression and intellectual impairment as part of Parkinson's disease, since 1966

- Pollok and Hornabrook, 1966: Dementia
- Warburton, 1967: Depression symptoms
- Mindham, 1970: Psychiatric symptoms
- Celesia and Wanamaker 1972: Psychiatric disturbancies
- Mayeux et al., 1981: Depression, intellectual impairment

Psychological factors in premorbid personality of PD

Sands, 1942

- premorbid habit:
  - externally calm, introverted
  - suppressing aggressive tendencies
  - hardly expressing their emotions
  - "Masked personality"

Depth Psychological Findings

Cohen-Booth, 1935; Mitscherlich, 1960; Korten and Ketterings, 1972:

- Readily subdue their own personal desires under social standards
- Strive for order
- Punctuality and cleanness
- Exhibit trends towards perfectionism
- Conservatism
- Rigid moral standards

Parkinson's Disease and Smoking

Bauman et al., 1979; Martilla and Rinne, 1980; Godwin-Austen et al., 1982)

Non-smokers, higher risk for PD:
- less adventurous, outgoing or decisive, more shy and unhappy

Smokers, lower risk for PD
- Impulsive, arousal seeking, danger-loving, risk-takers and belligerent against authority

Premorbid Personality of Parkinson Patients Innsbruck Group I

Poewe et al., 1983:
Examination with Giessen-Test (GT)
- Measurement of personality traits by self and foreign assessment,
  40 items in 6 standard scales for the features social resonance, dominance, control, basic mood, previousness, social potency (Beckmann and Richter 1972)

Results: Marked trends to over control, depressiveness, positive social resonance and social impotency

Tendency towards perfect fullfillment of task, towards order and punctuality while expecting the same from the persons of their surroundings.

Premorbid Personality of Parkinson Patients Innsbruck Group II

Poewe et al., 1990

used: mini-mental state (MMS) examination, Wechsler Adult Intelligence Scale (WAIS), intelligence quotient, VIQ plus subtests, Geriatric Depression Scale (GDS), Cattell's 16 PF semi-standardized biographical interview

- Results:
  - MMS, WAIS, VIQ, GDS
    - Introverted
    - depressed
    - pedantic
    - rigid
    - loners
    - teetotaler
  - 16 PF
    - more socially alert
    - apprehensive
    - self-reproaching
    - tensed
    - driven
    - restless
    - skeptical and cautious in their actual personality

Premorbid Personality of Parkinson Patients Innsbruck Group II

Poewe et al., 1990

PREMORBID PERSONALITY IN PD

Evaluation of semistandardized interviews into premorbid behavior and personality

Study groups	Depressed/ introverted	Workaholic	Pedantic	Rigid	Loner	Nonsmoker	Teetotaler
	Percent of experimentees scoring on item						
Controls (*N = 17*)	17.5%	55.5%	29.5%	14.5%	17.5%	49.5%	29.5%
	(11/24)	(41/70)	(24/35)	(12/17)	(11/24)	(41/58)	(24/35)
PD (*N = 38*)	49%*	71.5%	75%	50%	47.5%	66.5%	28%
	(48/50)	(50/85)	(74/75)	(42/58)	(45/50)	(61/72)	(27/29)

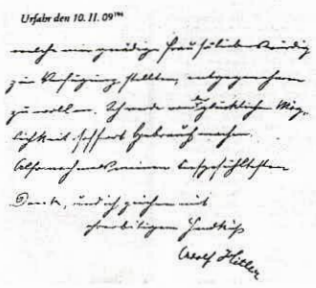
* p< 0.05 (PD vs controls)
Percentages given as means of two rating with indiviual ratings in brackets
PD. Parkinson's disease

PD in Leading Personality on the example of Adolf Hitler I

Gerstenbrand , Karamat, 1999

Hitler suffered from PD of equivalence type, severe tremor (left side), akinesia, rigidity
- First symptoms 1939: hypokinesia left arm
- Constantly increased after 1941
- Full symptoms 1944 after assassination attempt
- Severe PD in January 1945
  - Diagnosed by Prof. M. De Crinis, Neurologist, highest ranked SS physician
- Decision for treatment with special mixture with the knowledge of H. Himmler
- Hitler refused treatment afraid to be poisoned

PD in Leading Personality on the example of Adolf Hitler II



Hitler's handwriting, age of 20 years. Excessive rigidity, restrained motions, lack of flow and rhythm (old angular German handwriting)

PD in Leading Personality
on the example of Adolf Hitler III

Copy of a painting 19th century by A. Hitler, Michaelerplatz, Vienna

photo-like, without feeling of motion

PD in Leading Personality
on the example of Adolf Hitler IV

Scetch for a stage design "Lohengrin" by A. Hitler, rigid structures

PD in Leading Personality
on the example of Adolf Hitler V

Analysis of premorbid and morbid personality (physician examinations, various documentation, handwriting and painting analysis)

F. Gerstenbrand, E. Karamat, 1999

- Pedantic
- Anancastic
- Introverted
- Apprehensive
- Irresolute, undecided, wavering, hesitant
- Self-reproaching
- Sceptical
- Tension, restlessness
- Teetotaller
- Non-smoker
- Ahedonic
- Workaholic
- No tendency toward addictiveness
- Difficult relationship with women
- Urge for ceremonial ritual procedures

Obsessed by the idea to save Germany

Premorbid and morbid traits in Parkinsonian patients

Clinical features, test results, semistandardized interviews, graphomotor analyses

Clinical features

- Anancastic
- Pedantic
- Introverted
- Apprehensive
- Irresolute
- Undecided
- Wavering
- Hestiant
- Self-reproaching
- Sceptical

Clinical features

- Inner tension
- Restlessness

Social attitudes

- Ahedonic
- No tendency towards addictivness
- Difficult relationsship with other sex
- Loner
- Non-smoker
- Teetotaler
- Workaholic

Current ethical challenges in neurological practice

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EFNS TEACHING COURSE IN NEUROLOGY

Eger, Hungary
October 22-23, 2004

Ethics

Altruism
Sense of honour
Justness
Respect for others
Solidarity
Ability to forgive

Ethics:
Part of philosophy dealing with morality.

Moral
is search for an inner standard.

Kant's Categorical Imperative:
The individual should act in a way that his action can be regarded as general law.

Bioethical principles

Medical conduct, physicians obligations
(Belmont criteria, 1979)

- autonomy (of the patient)
- beneficence
- nonmaleficence
- justice
- (trust)

Kant's maxims

Autonomy
Dignity
Individual human rights

Western-Occidental ethics

- Aristotle philosophy – "the pure spirit", without any concept of God based on Plato and on the confrontation with biological-materialist thoughts (Pythagoras, etc.)
- Christian teachers - Saint Augustinus, Thomas Aquinas- introduced Christian elements, principle of one God
- Immanuel Kant postulated European moral and ethical norms in reflection of Aristotle philosophy
- Regional interpretation of ethics in Europe
  Existentialistic ethics (France)
  Value ethics – "Werte-Ethik"(Germany)
  Ethics of Marxism (Soviet Union)
  Theological ethics (East Europe)
- Bioethical rules as the adaptation to the technical development in modern medicine with the basis of principles of human rights
- No inclusion of the ethical rules of Buddhism, Konfucianism and the rules of the Islamic and the Mosaic religion
- No possibility for globalisation in the present state

Definition

Neuroethics is the application of the principles of bioethics in Neurology

World Medical Association Declaration of Helsinki, 1964 Ethical principles

- Ethical principle to provide guidance to physicians and other participants in medical research involving human subjects incl. identifiable material or identifiable data
- International code of medical ethics: The physician shall act only in patients interests when providing medical care which might have the effect of weakening the physical and mental condition of the patient
- Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects
- In medical research on human subject considerations related to the well being of the human subject should take precedence over the interest of science and society

The task of neuroethics

1. Ethics in research in Neurology
2. Neuroethics in clinical practice
3. Education in neuroethics
4. International conventions

Patient-doctor relationship

- Expectation of personal attention
- Trust
- Individualized treatment
- Best benefit to risk/ratio

- It is the patient right to finish the cooperation with his physician
- It is the physicians obligation to inform the patient of all the effects to initiate or to stop the running treatment (in written form)

Corpus Hippocraticum

Although it is the duty of the physician to cure patients completely and to reduce the frequency of diseases the physician should never attempt treatment of those who are already overcome by diseases or forthcoming age with somatic and mental reduction

Neuroethics in clinical practice

- New therapies
  - New drugs
  - New therapeutic devices
  - Implantation of human tissue in central nervous system (stem cells, embryonic tissues etc.)
  - Implantation of stimulating systems
- New diagnostic methods
- New neurosurgical methods
- Genetic testing and counselling
- Organ transplantation - selections of patients and donors
- Determination of brain death
- Palliative treatment of moribund patients
- Withholding of therapy in acute incurable conditions
- Withdrawing of life preserving measures in acute conditions
- Discontinuation of life support systems (end of life decision)

Current ethical issues in neurological practice

- Active euthanasia, free willingly, against free will
  medical assisted suicide
- Passive euthanasia, renunciation of acute treatment,
  renunciation of Maximal therapy
- Palliative treatment in terminal or moribund state of
  neurological diseases
- Withholding of Maximal therapy in incurable acute
  neurological conditions (severest brain damage)
- Decision for end of active neurorehabilitation
- End of life decisions in incurable neurological conditions
  (apallic syndrome/vegetative state without remission,
  final state in ALS, Alzheimer disease etc.)
- Resource allocation and adequate medical care (withholding
  of treatment of old patients, incurable cancer, etc.)
- Treatment of patients unable to consent
- Treatment of vulnerable persons (children, psychiatric patients)

Patients unable to consent
Decision making on behalf of patients

- Presumed consent in emergency situations
- Proxy consent by an authorized person,
  legal representative, solicitor
- Living will
  Advanced directives
  Previous expressed wishes
  Written will

Ethical issues in Neurology
New therapies

- Introduction of new drugs
- Introduction of new medical products
- Introduction of new therapeutic devices
- Implantation of human tissue in central nervous system including xenotransplantation
- Gene therapy
- Implantation of stimulating systems (brain, spinal cord)
- Introduction of new diagnostic methods
- Introduction of new neurosurgical methods

- Use of Evidence Based Medicine for diagnostic and therapeutic guidelines
- Use of diagnostic and therapeutic guidelines-COCHRANE library

Patients unable to consent
In clinical practice

The treating and responsible physician is often the true protector of the patient, who is incapacitated.

In research in case of conflicting interests
Protecting the research subject
Advancing medical knowledge

Patients unable to consent
(temporary-permanently)

» Basical legal prerequisite for every medical intervention: "Informed consent", better "valid consent"

» Values to be protected in decision making
Patients rights
Integrity
Dignity

Protection of vulnerable persons
Inability to consent in routine medical practice (reduced capacity)

- Children - parents or guardians as proxy
- Patients with cognitive impairment
  (Aphasia, etc.)
- Patients with progressive or terminal diseases
  (Alzheimer disease, MS, etc.)
- Patients in intensive care unit
- Apallic patients/vegetative state - full state or early remission

Ethical problems in neurorehabilitation

- End of active neurorehabilitation
  Transfer to nursing care, to home care
- Withholding of emergency care in acute complications in hopeless conditions,
  no "Maximal therapy"
- No research programs possible
  laboratory programs, etc.
- No use in donor's program
  plasma, etc.

Treatment of moribund patients

- W. Strauss, 1968: "To cure – sometimes; to relieve - often, to comfort - always".
- H. Küng, 1982: "Fighting death at any expense makes no sense, help becomes torture".
- T. Helme, 1996: "Ordinary terminal care involves a balance of sometimes conflicting "prima facie" duties to preserve life, to protect liberty, respect patients autonomy and to prevent suffering".

Brain death
European position

- Symptomatology, exact details
- Clinical course
- Clarification of the basic pathological process
- Additional examinations (EEG, TCD)
- Team of independent specialists
  neurologist-clinical symptoms
  anaesthesiologist-respiratory arrest
  EEG-specialist
- Exclusion of members from the transplantation team
- Minimal standard for developing countries
  WFN Guidelines

Evidenced Based Medicine

- a cultural and methodological approach to clinical practice helping to make decisions based on clinical expertise and an intimate knowledge of the individual patient's situations, beliefs, and priorities
- considered to be the scientifically grounded art of medicine
- it de-emphasizes intuition and unsystematic clinical experience as grounds for medical decision-making

Euthanasia
Eu-Thanatos = Easy Death

- Active euthanasia
  free willingly
  without free will,
  assisted suicide
- Passive euthanasia
  Withdrawal of therapy
  Withholding of therapy (active therapy, Maximal therapy)
  Discontinuation of life preserving measurements
- Voluntary euthanasia ("Zwangseuthanasie")

Evidence Based Medicine
Definition I

- Evidence based medicine involves integrating clinical expertise with the best available clinical evidence derived from systematic research.
- Individual clinical expertise is the proficiency and judgment that each clinician acquires through clinical experience and practice.

SE Straus, DL Sackett, 1998

Evidence Based Medicine
Definition II

The practice of EBM is a process of lifelong self directed learning in which caring for patients, creates a need for clinically important information about diagnoses, prognoses, treatment and other healthcare issues.

SE Straus, DL Sackett, 1998

Evidence Based Medicine
Critics II

- Cultural and methodological approach
- Converts the abstract exercise of reading and appraising the literature into a pragmatic process
- Internal bias
  - Economic-based interest
  - Inappropriately applied filters of literature
  - Only based on the positive results of evidence
- Epistemological approach identifies external bias
  - EBM can be changed or removed every time by relevant new or emerging evidence
  - Cannot be evaluated as the scientific "totem" of the third millennium

M Timio et al, 2000

Evidence Based Medicine
Definition III

- Best available clinical evidence is clinically relevant research which may be from the basic sciences of medicine, but especially that derived from clinical research
- patient centered
- evaluates the accuracy and precision of diagnostic tests and prognostic markers
- efficacy and safety of therapeutic, rehabilitative, and preventive regimens

SE Straus, DL Sackett, 1998

Evidence Based Medicine
Critics III

- "Evidence" in EBM must be of high quality in order to be useful but is not always the case
- "Real world" trials often do not give the same results as these highly artificial controlled clinical studies.
- EBM may be unreliable, sometimes giving different results to subsequent large randomized trials
- Bias in the hypotheses tested in large trials usually covered by commercially interested companies
- Process of journal review and publication is capricious, slow, may have a selection bias towards positive studies (communication channels for evidence are often unsatisfactory)
- For many rarer conditions there is no "high level" evidence (pediatrics, subspeciality surgeon, etc.)

DS Celermajer, 2001

- Usually no trials of old people who are on many pills

S Butterworth, 2004

Evidence Based Medicine
Critics I

- Among internal bias, economic-based interest may influence the development and diffusion of research and its results.
- difficulty to convert EBM into clinical practice recommendations- it is nearly impossible to make recommendations that are appropriate in every situation.
- EBM cannot be evaluated as the scientific "totem" of the third millennium, neither as the clinical digest of medical literature.

Evidence Based Medicine

- Clinicians are looking for new strategies to apply to diagnostic and therapeutic pathways and for the steps where EBM could be addressed when showing the full validity.

M.Timnio, D.Antiseri
Ital. Heart Journal (2000),1; 411-414

Cochrane Library

- Reviews are more systemic and less biased than systematic reviews published in paper journals
- Cochrane Collaboration has taken steps to improve quality of reviews
- Readers of Cochrane reviews remain cautious, especially regarding conclusions that favour new interventions

Critics:

- Neurological diagnoses are based on meta analysis of inhomogenous publications (phenomenologically and topically based)
- Experience based medicine gets more and more unessential

What is the Cochrane library

- Unique source of reliable and up-to-date information on the effects of interventions in health care.
- Health care relies not only on individual medical skills but also on best information
- Best information is compiled using the technique of evidence-based medicine
- The aim of the Cochrane library is to provide EBM information

Cochrane Website, 2004

Factors influencing European medicine

- Progress in research of biology and genetics
- Progress in basic research
- Progress in clinical medicine
- Increasing influence of ethical rules in clinical research
- Forced use of ICH-GCP in clinical trials
- Scarcity of resources
- Demographic developments
- Political changes in Europe
- Process of globalisation

- Trend to a predominance of Evidence Based Medicine
- Trend to the use of Cochrane library
- Loss of Experienced Based Medicine, loss of Traditional Medicine