CHIEF EDITOR DR. SYED MUBIN AKHTAR

KARACHI PSYCHIATRIC HOSPITAL

Regd. No. SS-237 BULLETIN APRIL 2012

THE GLOBAL DAY OF EPILEPSY

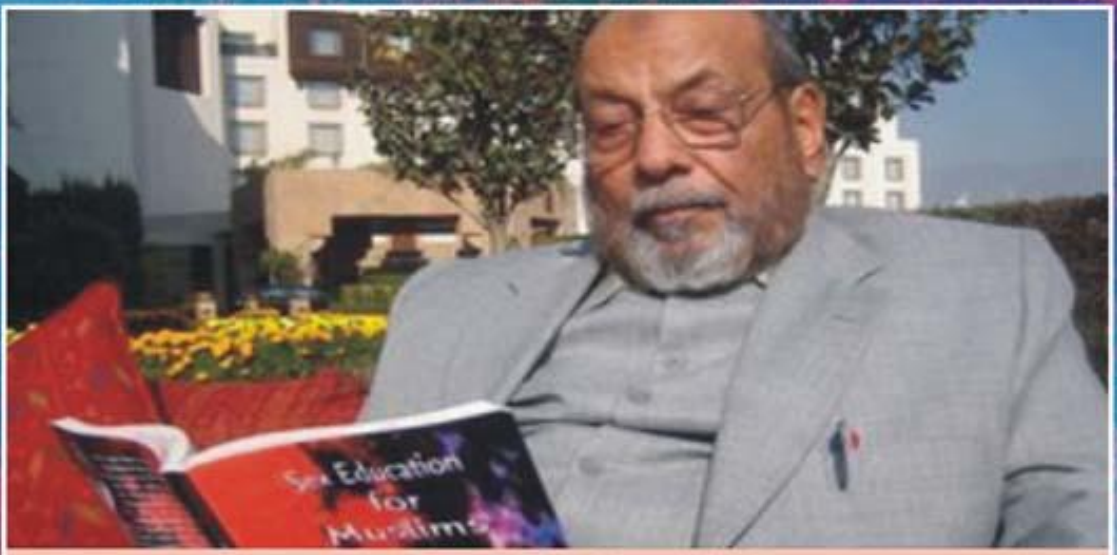
Estd. 1970

Seminar

عالمی یومِ مرگی

On 28th February 2012

Prof. Dr. Iqbal Afridi, Dr. Shahid Mustafa, Dr. Syed Mubin Akhtar and Syed Salahuddin speaking on the occasion of World Epilepsy Day.



DR MUBIN AKHTAR
ON A MISSION TO EDUCATE PAKISTANIS IN SEXUAL MATTERS

(From an interview by Aleem Maqbool BBC News)

The release of his book - **Sex Education for Muslims** - aims to teach people about sex in a way that is in keeping with Islamic instruction.

Dr Akhtar, 81, says the fact that sex is not discussed in Pakistan is having serious repercussions. As a psychiatrist, he says he has witnessed them himself, and that is why he felt the need to write his book.

"There's a huge problem in our country," he says.

"Adolescents, especially boys, when they get to puberty, and the changes that come with puberty, they think it's due to some disease.

"They start masturbating, and they are told that is very dangerous to health, and that this is sinful, very sinful."

'Misconceptions' - Dr Akhtar says he has seen cases where teenagers, not understanding what is happening to their bodies, have become depressed and even committed suicide. "I myself passed through that stage with all these concerns, and there's no-one to tell you otherwise, and that these are wrong perceptions. It was only when I entered medical college that I found out that these were all misconceptions." **"Ignorance about sexual matters is causing a lot of our young people unnecessary psychological distress."**

He says even now in Pakistan, many doctors do not discuss sexual matters openly, and that teachers and parents are embarrassed about the issues. **There is no sex education teaching in government schools.**

Dr Akhtar says it is not seen as appropriate to broach the subject of sex in the conservative culture of Pakistan, and that it is also felt that doing so might encourage young people to behave in an "un-Islamic" way.

"They ask me when you should start sex education, and I say as soon as the child can talk. They should be told the names of the genitals just as they are told about hands and eyes and ears, and nose," he says.

"When they get a little bigger and they ask where a child comes from, you can say it. That doesn't make the child sexually active or immoral." **Dr Akhtar says there is also nothing un-Islamic about discussing sex.**

He says he felt that the best way to help people understand that was to write a book which brought together basic sex education with information about the Islamic perspective on the subject.

"When I started to study what the Koran, Islamic law and religious scholars had to say about it, I realised there is so much discussion about sex in Islam. One would be surprised.

"There are sayings from the Prophet Muhammad about sexual matters, and historical sources tell us he answered detailed queries on the subject from both men and women."

The writings in Dr Akhtar's book are interspersed with quotes from the Prophet Muhammad, and also from the Koran, like this one: "You are allowed intercourse at night with your wives during the month of fasting. They are as intimate for you as your own clothes, and vice versa." (Koran, Surah Baqra, Verse 187)

'Quack'- Dr Akhtar writes of the Islamic thinking about masturbation, marital problems and how a man should wash himself after having sex so that he is clean enough to perform prayers. **Pakistani children have no access to sex education.**

Sex Education for Muslims is the name of the English version of the book, in Urdu the title is Special Problems for Young People.

KARACHI PSYCHIATRIC HOSPITAL

Vol.35 Issue No. IV APRIL - 2012 Regd. No. SS -237

MONTHLY BULLETIN

(Psychiatric Research Articles)

غریبوں کو کھانا کھلانا

یہ ایک بہتا چشمہ ہوگا جس کے پانی کے ساتھ اللہ کے بندے شراب پئیں گے اور جہاں چاہیں گے بسہولت اس کی شاخیں نکال لیں گے۔ یہ وہ لوگ ہوں گے جو (دنیا میں) نذر پوری کرتے ہیں، اور اس دن سے ڈرتے ہیں جس کی آفت ہر طرف پھیلی ہوئی ہوگی، اور اللہ کی محبت میں مسکین اور یتیم اور قیدی کو کھانا کھلاتے ہیں (اور ان سے کہتے ہیں کہ) "ہم تمہیں صرف اللہ کی خاطر کھلا رہے ہیں، ہم تم سے نہ کوئی بدلہ چاہتے ہیں نہ شکریہ، ہمیں تو اپنے رب سے اس دن کے عذاب کا خوف لاحق ہے جو سخت مصیبت کا انتہائی طویل دن ہوگا"۔

(قرآن۔ سورہ الدھر، 6 تا 11)

Readers are requested to send their articles, comments & suggestions.

Doctors who desire to get the bulletin should send their address, contact number and email to:

Address: B-1/14, Nazimabad # 3, Karachi-74600
Phone:111-760-760
Fax: 36681610
Email: editor@kph.org.pk
Email: support@kph.org.pk

CONTENTS

01	DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE	38
22	FORGIVENESS: A NOTE FOR PSYCHIATRISTS	59
25	MINDFULNESS TRAINING FOR SMOKING CESSATION: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL	62
26	OMEGA-3 FATTY ACID SUPPLEMENTATION FOR THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMATOLOGY: SYSTEMATIC REVIEW AND META-ANALYSIS	63
27	ASSESSMENT OF PEDOPHILIA USING HEMODYNAMIC BRAIN RESPONSE TO SEXUAL STIMULI	64
28	PROBLEM-SOLVING THERAPY AND SUPPORTIVE THERAPY IN OLDER ADULTS WITH MAJOR DEPRESSION AND EXECUTIVE DYSFUNCTION	65
29	INFLAMMATION, SANITATION, AND CONSTERNATION	66
30	COMPARATIVE BENEFITS AND HARMS OF SECOND-GENERATION ANTIDEPRESSANTS FOR TREATING MAJOR DEPRESSIVE DISORDER AN UPDATED META-ANALYSIS	67
31	A RANDOMIZED TRIAL EXAMINING THE EFFECTIVENESS OF SWITCHING FROM OLANZAPINE, QUETIAPINE, OR RISPERIDONE TO ARIPIPRAZOLE TO REDUCE METABOLIC RISK: COMPARISON OF ANTIPSYCHOTICS FOR METABOLIC PROBLEMS (CAMP)	68
32	COMPARATIVE EFFICACY AND ACCEPTABILITY OF ANTIMANIC DRUGS IN ACUTE MANIA: A MULTIPLE-TREATMENTS META-ANALYSIS	69
33	MAJOR DEPRESSION DURING AND AFTER THE MENOPAUSAL TRANSITION: STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)	70
37	بھارت کی خاتون کھلاڑی کا قبول اسلام	74

DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Adopted from an article in the National institute for health and clinical excellence

1 Guidance

This guidance applies to donepezil, galantamine, rivastigmine and memantine within the marketing authorisations held for each drug at the time of this appraisal; that is:

- donepezil, galantamine, rivastigmine for mild to moderately severe Alzheimer's disease
- memantine for moderately severe to severe Alzheimer's disease.

The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.

- The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:
- Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points (subject to section 1.2 below) and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect.
- In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:
  - where the MMSE is not, or is not by itself, a clinically appropriate tool for

assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties or

- where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

- When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions and dosing profiles.
- Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.
- Patients with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and patients with moderately severe to severe Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop.

II Clinical need and practice

- Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features.

- Alzheimer's disease is usually insidious in onset and develops slowly but steadily over a period of several years. It affects predominantly the elderly. Progression is characterised by deterioration in cognition (thinking, conceiving, reasoning) and functional ability (activities of daily living) and a disturbance in behaviour and mood. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition. Evidence suggests that Alzheimer's disease progression is dependent on age, and the time from diagnosis to death is about 5-20 years (median 5 years in people aged 75-80 years).
- People with Alzheimer's disease lose the ability to carry out routine daily activities like dressing, toileting, travelling and handling money and, as a result, many of them require a high level of care. Behavioural changes in the person, such as aggression, are particularly disturbing for carers.
- Non-cognitive symptoms in dementia include agitation, behavioural disturbances (for example, wandering or aggression), depression, delusions and hallucinations.
- Several different methods are used to assess the severity of Alzheimer's disease. These include: the Clinician's Interview-based Impression of Change (CIBIC) and CIBIC-plus for global outcomes; the Progressive Deterioration Scale (PDS) for functional/quality-of life scales; and the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog - 70 points) or the MMSE (30 points) for cognitive outcomes. MMSE score, for example, denotes the severity of cognitive impairment as follows:
  - mild Alzheimer's disease: MMSE 21-26
  - moderate Alzheimer's disease: MMSE 10-20
  - moderately severe Alzheimer's disease: MMSE 10-14
  - severe Alzheimer's disease: MMSE less than 10.
- Population data (2002) for England and Wales show an estimated prevalence of 290,000 people with Alzheimer's disease. On the basis of these figures a primary care trust (PCT) with a population of 200,000 might expect to have approximately 1100 cases of Alzheimer's disease. The incidence rate for Alzheimer's disease in people over the age of 65 years has been estimated at 4.9 per 1000 person-years in the UK. The incidence rate appears to have been stable over the past two decades and is found to be related to age (rising with increasing age) and gender (women have a higher risk than men). In people with Alzheimer's disease, 50-64% are estimated to have mild to moderately severe disease, and approximately 50% have moderately severe to severe Alzheimer's disease.
- People with mild dementia are sometimes able to cope without assistance, but as the disease

progresses, all eventually require the aid of carers, and about half need residential care. The total cost of care for people with dementia is estimated by the Audit Commission to be £6 billion per year in England, with half of this amount attributed to health and social services.

- People with dementia usually present to their general practitioner with memory problems, and an estimated 39% present to specialist clinics.

III The technologies

Acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine

- Acetylcholinesterase (AChE) inhibitors increase the concentration of acetylcholine at sites of neurotransmission.
- Donepezil (Donecept) is a specific and reversible inhibitor of AChE, licensed in the UK at a dosage of 5 mg/day and 10 mg/day. It is licensed for the symptomatic treatment of people with mild to moderately severe Alzheimer's dementia.
- Galantamine (Reminyl, Shire Pharmaceuticals) is a selective, competitive and reversible inhibitor of AChE, licensed in the UK. It is licensed for the symptomatic treatment of people with mild to moderately severe dementia of the Alzheimer type.
- Rivastigmine (Exelon, Novartis Pharmaceuticals UK) is an AChE and butyrylcholinesterase inhibitor, licensed in the UK. It is licensed for symptomatic treatment of people with mild to moderately severe Alzheimer's dementia. The usual maintenance dosage is 3-6 mg twice daily.
- Typical side effects of donepezil, galantamine and rivastigmine are related to the gastrointestinal tract (including nausea and vomiting). These side effects are dose related and although they are usually short term they can lead to non-adherence.

Memantine

- Memantine (Synaptol) is a voltage-dependent, moderateaffinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It is used in the treatment of people with moderate to severe Alzheimer's disease. The recommended maintenance dosage is 10 mg twice daily.
- In clinical trials in mild to severe dementia, involving patients treated with memantine and patients treated with placebo, the most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness, headache, constipation and somnolence. These adverse events were usually of mild to moderate severity. For full details of side effects and contraindications, see the summary of product characteristics.

IV Evidence and interpretation

The Appraisal Committee reviewed the

data available on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, having considered evidence on the nature of the condition and the value placed on the benefits of donepezil, galantamine, rivastigmine and memantine by people with Alzheimer's disease, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

- **Clinical effectiveness**

Mild to moderately severe Alzheimer's disease

- The quality of the reporting and methods of the included published randomised controlled trials (RCTs) of the AChE inhibitors (donepezil, galantamine and rivastigmine) was mixed.

Donepezil(Donecept)

- Thirteen published RCTs (aggregate number of people randomized 4200), one unpublished RCT and two systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of donepezil. (The original guidance included five RCTs, four studies from manufacturers and three systematic reviews.) Three of the new trials followed up participants for longer than 6 months.
- Six RCTs reviewed by the Assessment Group showed a statistically significant improvement in cognition following treatment with donepezil compared with placebo, as assessed using the ADAS-cog scale. Higher doses of donepezil were associated with increasing benefit. Three RCTs with a duration of 12-24 weeks contained data in a form that could be combined by the Assessment Group in a meta-analysis. A weighted mean difference of -2.51 (95% confidence interval [C I]-3.26 to 1.76) in terms of a change from baseline on the ADAS-cog was found for the 5 mg daily dose (aggregate number of people randomised 850) and a weighted mean difference of 13.01 (95% C I -3.91 to 2.10) was found for the 10 mg daily dose when compared with placebo (aggregate number of people randomised 608). An analysis based on the trial of 24 weeks' duration produced a mean difference in ADAS-cog change from baseline at 24 weeks of -2.88 (95% C I 0.5 to 1.2, $p < 0.0001$)
- Eight RCTs showed trends towards improved MMSE scores following treatment with donepezil compared with placebo. Results of a meta-analysis performed by the Assessment Group on two of these RCTs (aggregate number of people randomised 610) showed a change from baseline in MMSE score of 1.30 (95% CI 0.78 to 1.82) for 10 mg donepezil when compared with placebo. One UK study (486 people randomised), excluded from the metaanalysis by the Assessment Group, used MMSE as a secondary

outcome and showed that, over the first 2-year study period, the MMSE scores of the donepezil group were an average of 0.8 points higher than those of the placebo group (95% CI 0.5 to 1.2, p < 0.0001).

- Seven RCTs (aggregate number of people randomised 2460) assessed the effect of donepezil compared with placebo on global outcomes, using the clinical global impression of change (CGIC) or CIBIC-plus. There was a statistically significant greater change from baseline (improvement) in CGIC or CIBIC-plus scores following treatment with donepezil compared with placebo.
- Studies reporting on the effects of donepezil on functional outcomes in people with Alzheimer's disease (using a variety of measures of activities of daily living) generally found better, or less deterioration in, functional ability than for placebo, although these findings were not statistically significant in all of the trials. These trials generally measured changes in functional outcomes over treatment periods of 24 or 52 weeks. One UK study (486 people randomised) that measured rates of institutionalisation as a primary outcome for as long as 3 years found some differences between donepezil and placebo at 1 year (9% donepezil versus 14% placebo), although this difference was not statistically significant (p = 0.15) and not sustained at 3 years (42% donepezil versus 44% placebo, respectively, p = 0.4). Results for the other primary outcome - progression of disability - showed little difference at 1 year and no benefit at 3 years (13% donepezil versus 19% placebo at 1 year; 55% versus 53%, respectively, at 3 years); again these differences were not statistically significant.
- Quality-of-life estimates for people with Alzheimer's disease associated with the use of donepezil showed varied results, and only three studies reported on this outcome. Over the three studies, the impact of donepezil on this set of health measurements is unclear. One study showed improvement in quality of life, another showed no change and the third showed worsening of quality of life. The effect of the dose of donepezil used was unclear in all three studies.
- Behavioural symptoms were measured using the neuropsychiatric inventory (NPI) in four RCTs of donepezil. The results varied but generally a small and statistically significant effect was found for donepezil compared with placebo on improving or limiting further deterioration on the NPI scale in the short term.
- Adverse events were recorded more frequently in participants treated with donepezil compared with those receiving placebo, and numbers of adverse events increased with higher doses of donepezil. Similar numbers of participants in the low-dose donepezil groups and the placebo groups withdrew from the studies

because of adverse events. However, higher numbers of participants in the higher dose group withdrew because of adverse events.

- The manufacturer's submission included a 24-week RCT that evaluated the safety and efficacy of donepezil treatment compared with placebo in people with moderately severe Alzheimer's disease (baseline MMSE score 5-17). People receiving donepezil scored statistically significantly better on global, cognitive, functional and behavioural outcomes. A number of open-label and observational studies were also included in the manufacturer's submission. The effect size of donepezil on cognitive and global outcomes in these studies was similar to those recorded in the RCTs. The use of donepezil also appeared to show a benefit on outcomes such as 'delayed time to nursing home placement' and improvements in social behaviour (assessed by the carer).
- The manufacturer's submission and the assessment report included a study that aimed to establish the effect of continuation of treatment with donepezil (5 or 10 mg/day) for 153 people who had not shown a response ('no apparent clinical benefit') after 24 weeks of open-label donepezil treatment. Double-blind treatment was continued for 12 weeks and there was a statistically significantly greater mean improvement in MMSE score (1.62 versus 0.49) and NPI scale (-2.40 versus 0.76) following treatment with donepezil (10 mg/day) versus placebo, respectively.
- In further analyses using the manufacturer's intention to treat - last observation carried forward (ITT-LOCF) data from five RCTs of at least 24 weeks (aggregate number of people randomised 1425) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported in their review that 39% (95% CI 23% to 56%) of people on donepezil would have been a responder compared with 22% (95% CI 11% to 34%) on placebo. The magnitude of response of these responders on donepezil, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.26 (95% C I -7.80 to -4.72). The corresponding group of responders on placebo showed a magnitude of response of -5.27 (95% -6.90 t0 -3.64), while the non-responders on donepezil showed a magnitude of response of -1.21 (95% C I -2.11 t0o -0.30) and on placebo 0.99 (95% CI 0.04 to 1.94). When using an alternative definition of response (no change or improvement on ADAS-cog) the manufacturer reported a response rate of 63% for those people on donepezil and 41% for those on placebo. The magnitude of change from baseline compared with all

placebo reported by the manufacturer was -5.82.

- Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for donepezil a magnitude of change from baseline on ADAS-cog of -2.03 (99 C I -3.36 to -0.71) for people with mild Alzeimer's disease (MMSE of 21 or more; aggregate number of people randomised 546), of with moderate Alzheimer's disease (MMSE 15-20; aggregate number of people randomised 396) and of -3.63 (99% C I -7.98 to 0.72) for people with moderately severe Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 253) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people with mild cognitive impairment (ADAS-cog 4-28) was -3.24 (99% CI-7.10 to 0.62) and -3.91 99% C I -8.64 to 0.64) for people with moderate cognitive impairment (ADAS-cog 29-61). Comparable proportions of people were mild, moderate and moderately severe at baseline in the donepezil and placebo groups.
- Responder analyses for each of the three subgroups stratified according to cognitive impairment (based on MMSE) and using the responder definition of NICE technology appraisal guidance 19 resulted in 34% of the people using donepezil in the mild cohort, 31% in the moderate cohort and 10% in the moderately severe cohort retrospectively being designated a responder. The magnitude of response (analysis of observed cases) reported for these three subgroups was -5.12 (95% C I -6.82 to -3.43), -10.14 (95% C I -13.55 to -6.73) and - 6.32 (95% C I -13.11 to 0.47) for mild, moderate and moderately severe, respectively.
- In summary, evidence from studies using cognitive and global outcome measurement scales suggests that donepezil is beneficial in treating Alzheimer's disease. The effect of donepezil on quality of life and behavioural symptoms in Alzheimer's disease is less clear. Short-term benefits are seen on scales that measure functional outcomes but these were not always statistically significant and do not seem to be sustained in the long term. Retrospective responder analyses using NICE technology appraisal guidance 19 and subgroup analyses based on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Galantamine

- Seven published RCTs, one unpublished RCT (aggregate number of people randomised 4300) and one systematic review met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of galantamine. (NICE technology appraisal guidance 19 was based on one systematic review, three RCTs and three unpublished studies from the manufacturer.) All comparisons were versus placebo, with trials reporting dosages of 8-36 mg/day and durations of 3-6 months.
- All six published RCTs and the unpublished RCT assessed the clinical effectiveness of galantamine compared with placebo using the ADAS-cog scale. In all studies, galantamine conferred a statistically significant benefit to participants when compared with placebo. The benefit varied depending on the dose of galantamine.
- Four RCTs that assessed treatment with galantamine at a dose of 24 mg were combined by the Assessment Group in a metaanalysis. The fixed-effects model showed a weighted mean difference of -3.28 (95% C I -3.89 to -2.67) statistically significant improvement following treatment with galantamine versus placebo.
- Six RCTs assessed the effect of galantamine compared with placebo on the CIBIC-plus scale. They showed that, in individual studies, more participants on galantamine improved than on placebo (0-6.5 percentage points more), whereas more participants on placebo than on galantamine deteriorated (4-18 percentage points more). When the studies were pooled by the Assessment Group (aggregate number of people randomized 2294) no statistical significance was noted between treatment groups and placebo.
- The results of five RCTs showed that participants receiving galantamine at dosages of 16-32 mg/day had statistically significantly less deterioration than those receiving placebo, as assessed using scales that measure activities of daily living.
- In one RCT, higher dosages of galantamine (16 mg/day or over) were associated with a statistically significant slowing in the deterioration of participants' behavioural condition compared with placebo, as assessed using the NPI scale. In two trials, the slowing of deterioration was not statistically significantly different between galantamine and placebo groups.
- Across RCTs, between 2 and 27 percentage points more participants on galantamine experienced an adverse event compared with those on placebo. Between 6% and 44% of participants receiving galantamine withdrew from the studies because of adverse events, and this number increased with higher doses of galantamine.
- A number of open-label studies

included in the manufacturer's submission suggested a slightly reduced long-term decline in the cognition of people treated with galantamine.

In 6-week follow-on studies of two RCTs (aggregate number of people randomised 570), included in the manufacturer's submission, people who were switched from galantamine to placebo experienced a greater decline in measures of cognition than those who remained on galantamine. This difference reached statistical significance only in the study where the decision to stop treatment was not randomised (number of participants 500).

- In further analyses using the manufacturer's ITT-LOCF data fromfive RCTs of at least 24 weeks (aggregate number of people randomised 2682) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported that 41% (95% CI 31% to 51%) of people on galantamine would have been a responder compared with 27% (95% CI 20% to 35%) on placebo. The magnitude of response of these responders on galantamine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.40 (95% C I - 7.15 to -5.65). The corresponding group of responders on placebo showed a magnitude of response of -5.28 (95% C I - 5.93 to -4.63), while the non-responders on galantamine showed a magnitude of response of -0.44 (95% C I - 1.83 to 094) and placebo, 2.05 (95% CI 1.35 to 2.74). When using alternative definitions of response (no change or improvement on ADAS-cog and on global measures; no change, no improvement, or deterioration no more than 4 points on the ADAS-cog) a response rate of 57% and 87%, respectively, for those people on galantamine and 20% and 17%, respectively, for those on placebo was reported. The magnitude of change from baseline compared with all those on placebo by the manufacturer was -6.26 (95% C I - 6.87 to -5.66) and -4.33 (95% C I - 4.89 to -3.77) for the first and second alternative definitions of responders respectively.
- Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for galantamine a magnitude of change from baseline on ADAS-cog of -2.40 (99% C I - 3.33 to -1.47) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 938), of -4.1 (99% C I - 5.03 to - 3.17) for people with moderate Alzheimer's disease (MMSE 10-20; aggregate number of people randomised 1215; includes the moderately severe) and of -6.1 (99% C I - 7.93 to -4.27) for people with

moderate Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 340) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. Comparable proportions of people were mild, moderate and moderately severe at baseline in the galantamine and placebo groups.

- In summary, evidence from studies using cognitive and functional outcome measurement scales suggests that galantamine is beneficial in Alzheimer's disease. Improved benefits in cognition tended to be related to higher doses. Improvements in measurements of function were also demonstrated at higher doses. On global outcome measures, individual studies showed that higher proportions of participants improved with galantamine, but this was not reflected in the meta-analysis. In some studies, considerably more participants than those on placebo withdrew because of adverse events. Retrospective responder analyses using the NICE technology appraisal guidance 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Rivastigmine

- Four published RCTs (aggregate number of people randomized 1940), two unpublished RCTs (aggregate number of people randomised 1380) and three systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of rivastigmine. (NICE technology appraisal guidance 19 was based on three systematic reviews, five RCTs and two unpublished studies from the manufacturer.) All published comparisons were versus placebo, and trials reported dosages of between 1mg/day and 12 mg/day with durations of 26 weeks or less.
- **Four RCTs reviewed by the Assessment Group showed that rivastigmine within its licensed maintenance dose (6-12 mg/day, mean dosage approximately 10 mg/day) conferred a statistically significant benefit to participants when compared with placebo, as measured using the ADAS-cog scale. One RCT found no significant differences. No statistically significant effects were seen in the low-dose treatment groups in these studies.** A meta-analysis, using a fixed-effects model, of two RCTs both with a duration of 26 weeks, was associated with a weighted mean difference of -3.08 (95% C I - 3.78 to - 2.38) for rivastigmine 6-12 mg/day when compared with placebo. Statistically significant heterogeneity was found when pooling the two studies for meta-analysis, which led the

Assessment Group to conclude that the statistically significant treatment effect seen for rivastigmine in the fixed-effects model should be treated with caution.

- **Four RCTs showed statistically significantly higher MMSE scores in the groups treated with rivastigmine within its licensed maintenance dose regime (6-12 mg/day) compared with placebo.**
- **Four RCTs assessed the effect of rivastigmine compared with placebo on the CIBIC-plus scale. In the two published RCTs, statistically significant mean improvements were recorded following treatment with rivastigmine in the high-dose - licensed - regimen only, compared with placebo.** The percentage of improvers or responders on the CIBIC-plus scale was also calculated in these two published studies. Clinical improvement was defined as a score of 1, 2 or 3 on the CIBIC-plus scale. For the two trials, 16-20% of participants treated with placebo were judged to have responded versus 30-57% of those treated with rivastigmine. **A statistically significant difference was found for the high-dose regimen only.**
- Generally, participants treated with rivastigmine 6-12 mg/day demonstrated statistically significantly better functional outcomes than those who received placebo. One of the four studies using the PDS showed that there was no statistically significant difference for either the low- or high-dose regimen when compared with placebo.
- The Nurses Observation Scale for Geriatric Participants (NOSGER) was used in two rivastigmine RCTs. Statistically significant benefits were seen on the subscale that measures impact on memory but no statistically significant benefits were demonstrated on measures of mood and behaviour in the groups treated with rivastigmine compared with the placebo groups.
- The percentage of participants reporting adverse events, namely nausea and vomiting, resulting from treatment with rivastigmine was particularly high in those treated at a higher dose. The number of participants who withdrew because of adverse events was reported in all studies. **Estimates of the percentage of participants who withdrew varied considerably between studies; 7-28.6% for participants receiving treatment and 4-7.2% for participants receiving placebo.**
- The manufacturer's submission included a number of open-label and observational studies. The duration of these trials was between 26 weeks and 5 years. The effect size of rivastigmine on cognitive and behavioural outcomes was similar to that seen in the RCTs. Other open-label and observational studies, and experience with rivastigmine in a 'real-world' setting, appeared to show

some benefit in outcomes such as 'delayed time to nursing home placement' and carer burden.

- **The manufacturer's submission included a prospective, open-label study that evaluated the efficacy, safety and tolerability of rivastigmine in people who had failed to benefit from treatment with donepezil (because of a lack of efficacy [80%] or tolerability [11%], or both [9%]). After 26 weeks, 56% of the 382 participants had responded to rivastigmine (defined as improvement or stabilization of symptoms using the CGIC).**
- In further analyses using the manufacturer's ITT-LOCF data from four RCTs of at least 24 weeks (aggregate number of people randomised 1670) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported that 37% (95% CI 30% to 44%) of people on rivastigmine would have been a responder compared with 24% (95% CI 18% to 30%) on placebo. The magnitude of response of these responders on rivastigmine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.83 (95% C I - 8.25 to - 5.40) corresponding group of responders on placebo showed a magnitude of response of -5.57 (95% C I - 6.49 to - 4.65) while the non-responders on rivastigmine showed a magnitude of response of -4.0 (95% C I - 1.94 to - 1.13) and on placebo, 1.81 (95% C I - 1.07 to 2.55).
- Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for rivastigmine a magnitude of change from baseline on ADAS-cog of -1.20 (99% C I -2.10 to - 0.30) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 734), -3.7 (99% C I - 5.13 to - 2.27) for people with moderate Alzheimer's disease (MMSE 10-20; aggregate number of people randomised 557) and of -5 (99% C I - 7.40 to - 2.6) for people with moderately severe Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 232) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people within a number of strata for cognitive impairment was -0.4 (99% C I - 1.37 to 0.57) (ADAS-cog was 0-12), -1.7 (99% C I - 2.85 to 0.55) (ADAS-cog was 13-20), -2.6 (99% C I - 4.22 to -0.95) (ADAS -cog 21-28), -4.9 (99% C I - 7.28 to 2.52) (ADAS-cog 29-36), -5.9 (99% C I - 8.86 to -2.94) (ADAS -cog 37- 44) and -3.9 (99% C I - 7.38 to -0.42) (ADAS -cog 45 plus).

Comparable proportions of people were

mild, moderate and moderately severe at baseline in the rivastigmine and placebo groups.

- In summary, a range of fixed and flexible dosing regimens of rivastigmine was investigated across studies, which makes interpretation of the evidence more difficult. **Evidence from studies using cognitive and global outcome measurement scales suggests that rivastigmine is beneficial in Alzheimer's disease at higher doses (6-12 mg). Evidence for an effect on functional outcomes was less conclusive and no statistically significant benefit of rivastigmine on measures of behaviour and mood was reported.** Higher doses of rivastigmine were associated with considerable adverse effects and these effects caused withdrawals from studies. The results of the meta-analysis on cognition should be treated with caution because of statistically significant heterogeneity between individual trial results. Retrospective responder analyses using the NICE technology appraisal guidance 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Head-to-head comparisons

- Three RCTs met the inclusion criteria for the systematic review by the Assessment Group. Two compared donepezil with rivastigmine (aggregate number of people randomised 139) and one compared donepezil with galantamine (people randomised 120). The Assessment Group regarded the quality of the studies as generally poor. The manufacturer's submission for galantamine included a study comparing galantamine with donepezil, but this study was excluded by the Assessment Group because the study population was not described as patients with mild to moderately severe Alzheimer's disease by any definition and the MMSE scores fell outside the range of 10-26.
- **For the two RCTs that compared donepezil with rivastigmine, the difference in change from baseline, in measures of cognition or function, was small and not statistically significant. The number of adverse events tended to be higher in participants in the rivastigmine groups.**
- In the RCT that compared galantamine and donepezil, which was sponsored by the manufacturer of donepezil, participants on galantamine showed improvement on measures of cognition and function but the improvement in participants on donepezil was greater. However, in the comparison that was funded by the manufacturer of galantamine this effect seemed to be reversed and it appeared that galantamine exerted a

more sustained effect than donepezil.

Moderately severe to severe Alzheimer's disease Memantine(Synaptol)

- Two RCTs (aggregate number of people randomised 650) met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of memantine. (NICE technology appraisal guidance 19 did not consider memantine.) Both studies reported on participants with moderately severe to severe Alzheimer's disease, as measured by the MMSE, and treated with memantine 20 mg/day. One study compared memantine alone with placebo over a period of 28 weeks, and the other compared memantine plus donepezil with donepezil alone over 24 weeks. In the second study, participants were included on the basis that they had already been receiving donepezil for more than 6 months before entering the trial, and they had been at a stable dosage (5-10 mg/day) for at least 3 months. These participants were maintained on stable donepezil for the duration of the study. The quality of reporting and methods of the two trials was generally good.
- **In the RCT of memantine versus placebo, less deterioration of cognitive function was recorded following treatment with memantine compared with placebo, as measured by the Severe Impairment Battery (SIB)** (mean change from baseline at end point LOCF analysis for memantine and placebo was !C#@&4,/&!%@#%J& respectively, p < 0.001), the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) (mean changes from baseline at end point LOCF analysis: !:#%&4,/&!$#"J&G = 0.02) and the Functional Assessment Staging scale (FAST) (mean changes from baseline at end point LOCF analysis: 0.2 and 0.6, p = 0.02). No statistically significant differences were recorded using CIBIC, MMSE and NPI when changes from baseline to end point were analysed using LOCF.
- **In the RCT in which participants received memantine and donepezil in combination, less deterioration in cognitive function was recorded in participants receiving combined treatment compared with donepezil alone.**
- The manufacturer of memantine also provided summary results from a number of pooled analyses. In one analysis, data for all three RCTs showed less deterioration in cognitive function for patients receiving memantine.
- Similar pooled analyses were undertaken for patients who were subclassified as 'behaviourally disturbed', defined as a score > 0 on any of the NPI sub-item scores for three specific items: agitation/aggression; delusions and hallucinations. Patients had to score >

0 on any of the three items at baseline to qualify. For the analyses containing all three RCTs, less deterioration in cognitive function for patients receiving memantine.

- Memantine's manufacturer also supplied a 'responder analysis', which itself was restricted to further consideration of only the 'behaviourally disturbed' subgroup, where a responder was defined as an improvement or no worsening of CIBIC-plus scores at 6 months using data from all three RCTs.
- A fourth RCT was also referenced by the manufacturer of memantine. This compared memantine with placebo, and a proportion (n = 79, 48%) of participants had moderately severe to severe Alzheimer's disease. Although different outcome instruments were used in this trial, the results were broadly in line with findings from the other three RCTs.
- The frequency of overall adverse effects was similar for both the memantine and control groups in all RCTs.

Mild to moderately severe Alzheimer's disease Donepezil(Donecept)

- Eleven economic evaluations for donepezil were found. Three related to the UK. One of the 11 studies was of treatment for people with mild Alzheimer's disease; the other 10 were of treatment of people with mild to moderate Alzheimer's disease. **In 5 (of 11) studies donepezil was found to be cost saving.**
- In a UK study associated with the manufacturer, the cost of gaining an additional year in a non-severe state was measured. The estimated cost ranged from £1200 to £7000, depending on dose and starting point (mild or moderate Alzheimer's disease).
- In a recent economic analysis alongside a clinical trial, the authors concluded that the drug was not cost effective, mainly because there were no apparent benefits of the drug in delaying progression of disability or entry to institutional - that is, residential - nursing or NHS continuing care.
- The manufacturer's model used a transition state modeling approach in which disease progression was modeled across different levels of Alzheimer's disease severity to estimate the incremental cost effectiveness of donepezil compared with placebo. Transition probabilities were derived from trial data, with the drug efficacy rate persisting for the initial 12-month cycle of the model. For the remainder of the 5-year model, the transition probabilities for the treated group were proportional to those of the placebo group. Cost estimates were taken from the literature in which they were calculated for different severity levels of Alzheimer's disease by MMSE score. The submission reported that, for the base case of people with an MMSE score of 13-26, treatment with

donepezil 10 mg/day was associated with an estimated cost of £1200 to keep a person outside of the severe Alzheimer's disease state for a year. Inclusion of people with an MMSE score of 10-12 increased this to £4000 per year outside of the severe state. The manufacturer's model allowed for estimates of CQG to be calculated but did not report utility estimates or results in terms of CQG either in the base case analysis or in the sensitivity analyses.

Galantamine

- Five economic evaluations for galantamine were found. One related to the UK. All published economic evaluations on galantamine used the same method for modelling disease progression - the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model.
- All studies estimated that galantamine was cost saving for moderate Alzheimer's disease. For mild Alzheimer's disease, four studies showed galantamine to be cost saving, and the fifth, a UK study, was associated with a CQG for galantamine of £9000.

Rivastigmine

- Five economic evaluations for rivastigmine were found, one of them in abstract form only. Two related to the UK. All were of people with mild to moderate Alzheimer's disease. Four, including all three industry-associated studies, were found to be cost saving.
- In a study supported by the manufacturer, for people using the drug compared with not using it, estimated cost savings (but not including the cost of rivastigmine) after 2 years were £1300 for people with mild Alzheimer's disease and £800 for those with moderate Alzheimer's disease.

ASSESSMENT

- An augmented base case for the Assessment Group model was formulated that included alternative cost estimates and all extra health benefits mentioned in section 4.2.6.1, as well as the increase in utility for pre-full-time care. When the cost component of the augmented base case was compared with the cost estimates of the Assessment Group base case there was no substantial difference between the two. Estimates of CQG presented here for the augmented base case use the assumption that 70% of costs of institutional care are being met by the NHS/PSS (Personal Social Service). The complete augmented base case was associated with an estimated CQG of £54,000, £46,000 and £39,000 for donepezil, galantamine and rivastigmine, respectively (including a correction for the coefficient 'age at onset' used in the risk-equation for 'fulltime care', a price adjustment for donepezil and an adjustment in the results of the meta-analysis of effectiveness for galantamine). This equates to a

respective average QALY gain of 0.058, 0.062 and 0.060.

- There is very little quantitative evidence related to carer utilities and the evidence that exists suggests that utility scores for the carers were insensitive to people's Alzheimer's disease stage and setting. When an assumed 0.01 of carer utility was included in a sensitivity analysis on the augmented base case, either as a direct benefit or as part of the total increment between the two health states of the Assessment Group's model, this was associated with marginally lower estimates of the CQG: £50,000, £44,000 and £36,000 for donepezil, galantamine and rivastigmine, respectively.
- In the one-way sensitivity analysis on mortality on the augmented base case, a change in annual mortality rate only marginally affected CQG estimates. A range of estimates of the prevalence of neuropsychiatric or behavioural symptoms was used to assess the impact on the CQG estimates. On its own, changing the estimates of effects of therapy on neuropsychiatric or behavioural symptoms.

Decision Support Unit report

- The Decision Support Unit (DSU) evaluated the issues identified by consultees and considered that four issues were related to the economic model's technical reliability and required amending in the model. These were:
  - implementing the hazard for transition to full-time care
  - separating the characteristics of uncertainty and variability in the model
  - implementing discounting
  - implementing the augmented benefit

Each of these issues was corrected in the model. In addition their cumulative impact was examined.

Hazard for transition to full-time care

- The DSU considered that an instantaneous hazard rate for the transition to full-time care had been treated as a probability. For mild disease, correcting this changed the ICER from £63,749 to £63,164 per QALY gained (donepezil) and from £59,108 to £59,500 per QALY gained (galantamine). For moderate disease correcting this changed the ICER from £31,550 to £31,556 per QALY gained (donepezil).

Sampling of patient characteristics

- The probabilistic sensitivity analysis included both variables that were intrinsically unknown for any patient and variables that were known but subject to variation. The DSU set all patient characteristics to their mean value, and created subgroups by ADAS-cog score and age at starting treatment. For mild disease treated with donepezil, the base-case ICER was £63,749 per QALY gained. Three age subgroups were created (64, 70

and 74 years) and the ICERs for each of these subgroups were £84,659, £73,804 and £55,779 per QALY gained, respectively. For mild disease treated with galantamine, the base-case ICER was £59,108 per QALY gained.

Memantine (Synaptol)

- Five economic evaluations were found for memantine in people with moderately severe to severe Alzheimer's disease; three were in abstract or poster form, and the other two were in press. One of the five evaluations related to the UK. **All suggested that memantine was more effective and less costly compared with no treatment.**
- The manufacturer submitted a second economic evaluation, which compared the use of memantine in combination with donepezil against donepezil monotherapy. Most of the methods, results and accompanying discussion were marked commercial-in-confidence.

The model suggests that memantine plus donepezil is more effective and less costly compared with donepezil alone.

Acetylcholinesterase inhibitors: donepezil, galantamine and rivastigmine

- The Committee heard that since NICE technology appraisal guidance 19 was issued in 2001, the evidence base relating to the use of the AChE inhibitors has matured and continues to demonstrate that, compared with placebo, the AChE inhibitors provide small but consistent gains in scores on cognitive and global scales for people with mild to moderately severe Alzheimer's disease. The Committee noted, however, that the evidence available on the long-term effectiveness of the AChE inhibitors on outcomes, such as quality of life and delayed time to nursing home placement, was limited and largely inconclusive.
- The Committee considered the acquisition costs, the range of clinical effectiveness estimates, the different side-effect profiles and the results from direct comparisons between the AChE inhibitors. It concluded that it would not be appropriate to differentiate between the drugs on the basis of their effectiveness, but in the light of its responsibility to take account of the effective use of NHS resources, the Committee considered that it was appropriate to indicate that prescribers should take into account the acquisition costs of each AChE inhibitor when considering which of the AChE inhibitors to prescribe as well as other factors pertinent to the choice of an individual AChE inhibitor such as adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions, and dosing profiles.
- Having considered all the evidence and the comments of consultees, the Committee concluded that the resulting estimates of cost

effectiveness could be considered sufficiently acceptable to suggest that the prescribing of AChE inhibitors for people with Alzheimer's disease and moderate cognitive impairment (MMSE scores between 10 and 20) is cost effective.

Handling of variables in the economic model

- The Committee accepted comments from consultees that note that the model calculates the transition to full-time care as a hazard but subsequently applies this as if it was a probability. The Committee noted the DSU's correction of this and accepted that this resulted in minimal changes to the ICERs for the population of people with mild Alzheimer's disease.
- The Committee accepted the methodological comment from consultees that the model conflates heterogeneity in the patient population with uncertainty by including in the probabilistic sensitivity analysis values which are intrinsically known for each patient, but subject to variation (for example, age). The Committee noted both the consultees' and the DSU's explorations of this issue in subdividing the patient population by age and cognition and concluded that the consultee and DSU age stratification (but see 4.3.26) of people with mild Alzheimer's disease did not result in the generation of ICERs within the normally accepted range, without making further changes to parameter estimates. The Committee further heard from the DSU that other exploratory analyses of the model using alternative approaches to separating variability from parameter uncertainty (for example, using a weighted average of the costs and QALYs for the different age groups or separating out the sampling of patient characteristics from the sampling of parameter uncertainty) had led to similar estimates of the ICER as those in the augmented base case. Overall, the Committee was not persuaded that the sampling of patient characteristics had led to an overestimation of the ICERs. In addition, the Committee considered that there was no evidence of differential effectiveness of the AChE.

Memantine (Synaptol)

- For moderately severe to severe Alzheimer's disease, the Committee considered evidence from three trials of memantine (including evidence from one trial that was submitted after the assessment report was completed). The results from pooled analyses of these data were also considered, as were the results from a fourth RCT in which a subgroup comprised patients with moderately severe to severe Alzheimer's disease. The Committee also took into account the submitted economic evidence.
- The Committee noted that for the two memantine monotherapy trials (in which the majority of patients had Alzheimer's disease) the results were

inconsistent, with the late submission of a trial having statistically non-significant results on all scales. Although data from the pooled analysis of these two memantine monotherapy RCTs and a pooled analysis of the three RCTs versus placebo showed statistically significant advantages (at the 95% level) on a number of outcomes, the absolute magnitude of difference on all outcomes was modest.

- Overall, considering the published and unpublished evidence, the Committee concluded that the evidence to determine the clinical effectiveness of memantine in either the whole population of moderately severe to severe Alzheimer's disease or the subgroup of people with behavioural symptoms was currently insufficient. Nevertheless, irrespective of this conclusion, the Committee sought to consider the cost-effectiveness calculations that might be derived from these limited data.
- However, in this scenario an average of 22% and 45% of patients who received memantine and no treatment, respectively, progressed from moderately severe to severe disease at the end of one (Markov) cycle.
- **The Committee therefore concluded that on the basis of current evidence on clinical effectiveness memantine could not reasonably be considered a cost-effective therapy for moderately severe to severe Alzheimer's disease.**

FORGIVENESS: A NOTE FOR PSYCHIATRISTS

Prakash Gangdev

Department of Psychiatry, University of Western Ontario and Mood and Anxiety Disorders Program, Regional Mental Health Centre-London

Although forgiveness has received a lot of attention in the past two decades and its role in physical and mental health is being increasingly recognized, psychiatrists are unaware of its therapeutic benefits. A literature review was conducted with a view to create awareness of the recent advances in forgiveness research. Although forgiveness has been shown to be beneficial, more research is required, especially in the psychiatric setting. The role of resentment and bitterness in the causation of psychiatric disorders remain largely unevaluated and requires further study.

"The man who opts for revenge should dig two graves."
(A Chinese Proverb)

Forgiveness is traditionally a concept that is embedded in religion and all the major religions discuss forgiveness. Philosophers and ethicists have debated on this topic and forgiveness has been conceptualized, both as a value and as a weakness. The post conflict reconciliation phenomenon in primates indicates that human forgiveness has an evolutionary significance in that there is a need for adaptation by cooperation in order to maintain social stability, and this can only occur if revenge seeking is replaced by forgiveness. Politicians who have been held in saint-like reverence, like Mohandas Gandhi, Martin Luther King, Jr., and Nelson Mandela all practiced forgiveness, and the Truth and Reconciliation Commission in South Africa is an example of state-mediated amnesty program driven by forgiveness. Equally telling are the genocides such as the one in Rwanda, where revenge instead of forgiveness was in operation. The role of forgiveness in peace has been reviewed by O'Connell.

The aversion of the social sciences to forgiveness was eroded with the publication of a book (Forgive and Forget: Healing the Hurts We Don't Deserve) by Lewis Swede, a theologian, who spurred an interest that led to empirical studies. Developmental, social, health, and personality psychologists, all began studying and promoting forgiveness.

Clinical applications of forgiveness as a therapeutic intervention were also published. The International Forgiveness Campaign and funded research on forgiveness in the past two decades have created a greater awareness of forgiveness. The Internet offers numerous resources and a number of organizations are engaged in promoting forgiveness, both as a sociopolitical and as a clinical intervention.

Benefits of Forgiving

Forgiveness is associated with improved physical health and mental health. Psycho physiological and neuroimaging studies demonstrate the possible biological underpinnings of forgiveness. Forgiveness has been employed as an educational tool with beneficial effects and has also been shown to be beneficial for victims of abuse and unfaithfulness. Thus, forgiveness is not only a virtue and a moral act, but it also has therapeutic potential.

Lack of Awareness and Skepticism

Surprise and skepticism were expressed by other health professionals at case conferences for these patients, and at a journal club, when a paper on forgiveness was presented to a group of psychiatrists there was a similar lack of awareness. Likewise, in a discussion with therapists working in a trauma program, a large number were very opposed to the idea of forgiveness as being of any therapeutic value for their patients.

Clinical Implications for Psychiatrists

Given the neglect and a lack of awareness, it is time to call the attention of psychiatrists to forgiveness. Notwithstanding the lack of consensus about the definition of forgiveness and the associated theoretical models, it may be defined as releasing or foregoing of bitterness and vengeance by a victim toward the perpetrator of an offence, while acknowledging the seriousness of the wrong. Forgiveness is distinct from pardon, condoning, forgetting, and reconciliation. Self-forgiveness is the willingness to abandon self-resentment in the face of one's own acknowledged objective wrong, while fostering compassion, generosity, and love toward oneself. **A slight departure (with possible significant implications for psychiatry) occurred in the definition provided by DeShea and Wahkinney: self-forgiveness is a process of releasing resentment toward oneself for a perceived transgression and wrongdoing.**

A range of emotions (anxiety, hurt, sadness, hostility, and anger), cognitions (revenge seeking, ruminations, and cognitive rehearsal), and behaviors (grudge-bearing, avoidance of the perpetrator, demands for atonement) occur when a person is mistreated or victimized. Depending on the context and the personality factors, there may be open expression of the feelings, or the anger is muted, paving way for resentment which has been linked to psychopathology and may underlie

various psychiatric conditions. Resentment per se is not considered a diagnosis.

The Indian Perspective

All religions practiced in India emphasize the value of forgiveness. Religion plays a significant part in our lives and seeking forgiveness and forgiving are easily understood concepts to most Indians. The Mahabharata glorifies forgiveness. Jains observe Kshamavani Divas seeking and granting forgiveness. Forgiveness is also mentioned in Buddhist, Christian, and Sikh scriptures, and Quran. The stories of a Buddhist monk who upon being chopped, only experienced compassion for the king who ordered his torture, and King Ashoka extolling forgiveness after his conversion to Buddhism are well-known examples in Buddhist literature.

Editor's note: On a personal level Islam allows revenge equivalent to the hurt caused but considers forgiveness as more pious. In the case of criminals no forgiveness is expected. However in the case of murder the murderer can escape the death penalty if the family of the deceased forgives the perpetrator either with or without compensation.

The prophet (PBUH) stated that "Help the tyrant oppressor as well as oppressed." Asked how to help the tyrant oppressor, he replied "Stopping him from oppressing is the way to help him." This is what Jehad is about apart from defense of a nation, any nation, from attacks. Thus forgiveness is well and good for personal conflicts but force must be used to prevent tyranny, oppression or invasion and exploitation.

The prophet (PBUH) stated that "if one does not confront the oppressing tyrant and lets the oppressed person/s suffer then he will be considered as responsible as the oppressor himself."

---

http://www.indianjpsychiatry.org/text.asp?2009/51/2/153/49459

MINDFULNESS TRAINING FOR SMOKING CESSATION: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

Brewer JA et al - Drug Alcohol Depend 2011 Jun 30

Mindfulness training (MT) has been incorporated into cognitive therapy, relapse prevention, and acceptance and commitment therapy for smoking cessation. This 4-week, randomized, controlled study tested the efficacy of MT as a stand-alone treatment.

Eighty-eight smokers interested in quitting (mean age, 46; 62% men; average use, 20 cigarettes/day; mean previous quit attempts, 5) underwent MT or the American Lung Association's Freedom From Smoking (FFS) program, a manual-based and validated smoking cessation treatment. People on psychotropic medications or with comorbid substance use disorders were excluded. Both treatments involved twice-weekly group sessions for 4 weeks; follow-up occurred through week 17. MT focused on awareness and acceptance of cravings and on negative affect, such as anxiety or stress.

In both groups, cigarette use was significantly reduced during treatment and follow-up. MT was associated with greater smoking reductions than FFS during both periods. A trend toward higher abstinence rates with MT at the end of treatment (36% vs. 15% with FFS) became significant at 17 weeks (31% vs. 6%).

Comment: MT shows promise as a stand-alone treatment for smoking cessation. Further studies are necessary to determine whether MT is effective for smoking cessation in psychiatric patients. In another study, greater mindfulness was associated with lower levels of craving, perceived stress, and laboratory-tested attentional bias towards alcohol-related images in 58 recovering alcohol-dependent adults (Cognit Ther Res 2011). Together, these studies suggest that mindfulness may benefit patients with substance use disorders by increasing their acceptance of, and ability to cope with, cravings and negative affect. Given its efficacy for anxiety and depression as well, MT appears a useful treatment for mental health clinicians to learn.

(http://dx.doi.org/10.1016/j.drugalcdep.2011.05.027)

OMEGA-3 FATTY ACID SUPPLEMENTATION FOR THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMATOLOGY: SYSTEMATIC REVIEW AND META-ANALYSIS

Bloch MH and Qawasmi A-J Amer Acad Child Adolesc Psychiatry 2011 Aug 16

Increasing evidence for the efficacy of omega-3 polyunsaturated fatty acids for neuropsychiatric illnesses, and some parents' preference for nonpharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) in their children, led these investigators to conduct a meta-analysis of studies of omega-3s for ADHD symptoms.

Potential studies were screened for rigorous study criteria, including use of ADHD severity scales, randomization, and blinded raters and excluding the initiation of another alternative or drug treatment during the study. The researchers identified 10 reports that included 699 children (range of mean ages, 9-12 years; 60%-87% male; study duration, 7 weeks to 4 months). Eight studies involved monotherapy, and two involved augmentation of stable ADHD therapy. Omega-3s were eicosapentaenoic acid (EPA; 750 mg) or docosahexaenoic acid (DHA; 480 mg). For placebo, nine studies used palm, olive, canola, or sunflower oil. One study compared the omega-3 precursor alpha-linolenic acid (120 mg) with vitamin C.

Only EPA was significantly more efficacious than placebo, both overall and for hyperactivity and attention symptoms separately, but had a small effect size (0.31). Higher EPA dose was significantly associated with greater response. Study type (monotherapy or augmentation), placebo type, study quality on a standardized scale, and duration did not affect outcomes.

Comment: These promising findings for a nonpharmacological intervention are tempered by the effect size, which is small compared with that for stimulants. But baseline measures of these fatty acids were not included. A larger effect size might be evident if only children with low baseline levels were included. Measuring baseline fatty acids and examining a range of EPA doses would be useful in future studies.

(http://dx.doi.org/10.1016/j.jaac.2011.06.008)

ASSESSMENT OF PEDOPHILIA USING HEMODYNAMIC BRAIN RESPONSE TO SEXUAL STIMULI

Jorge Ponseti, PhD and colleagues - Arch Gen Psychiatry

Context Accurately assessing sexual preference is important in the treatment of child sex offenders. Phallometry is the standard method to identify sexual preference; however, this measure has been criticized for its intrusiveness and limited reliability.

Objective To evaluate whether spatial response pattern to sexual stimuli as revealed by a change in the blood oxygen level-dependent signal facilitates the identification of pedophiles.

Design During functional magnetic resonance imaging, pedophilic and nonpedophilic participants were briefly exposed to same- and opposite-sex images of nude children and adults. We calculated differences in blood oxygen level-dependent signals to child and adult sexual stimuli for each participant. The corresponding contrast images were entered into a group analysis to calculate whole-brain difference maps between groups. We calculated an expression value that corresponded to the group result for each participant. These expression values were submitted to 2 different classification algorithms: Fisher linear discriminant analysis and -nearest neighbor analysis. This classification procedure was cross-validated using the leave-one-out method.

Setting Section of Sexual Medicine, Medical School, Christian Albrechts University of Kiel, Kiel, Germany.

Participants We recruited 24 participants with pedophilia who were sexually attracted to either prepubescent girls (n = 11) or prepubescent boys (n = 13) and 32 healthy male controls who were sexually attracted to either adult women (n = 18) or adult men (n = 14).

Main Outcome Measures Sensitivity and specificity scores of the 2 classification algorithms.

Results The highest classification accuracy was achieved by Fisher linear discriminant analysis, which showed a mean accuracy of 95% (100% specificity, 88% sensitivity).

Conclusions Functional brain response patterns to sexual stimuli contain sufficient information to identify pedophiles with high accuracy. The automatic classification of these patterns is a promising objective tool to clinically diagnose pedophilia.

PROBLEM-SOLVING THERAPY AND SUPPORTIVE THERAPY IN OLDER ADULTS WITH MAJOR DEPRESSION AND EXECUTIVE DYSFUNCTION

George S. Alexopoulos, MD; Patrick J. Raue, PhD; Dimitris N. Kiosses, PhD; R. Scott Mackin, PhD; Dora Kanellopoulos, BS; Charles McCulloch, PhD; Patricia A. Areán, PhD

Context Older patients with depression and executive dysfunction represent a population with significant disability and a high likelihood of failing pharmacotherapy.

Objectives To examine whether problem-solving therapy (PST) reduces disability more than does supportive therapy (ST) in older patients with depression and executive dysfunction and whether this effect is mediated by improvement in depressive symptoms.

Design Randomized controlled trial.

Setting Weill Cornell Medical College and University of California at San Francisco.

Participants Adults (aged >59 years) with major depression and executive dysfunction recruited between December 2002 and November 2007 and followed up for 36 weeks.

Intervention Twelve sessions of PST modified for older depressed adults with executive impairment or ST.

Main Outcome Measure Disability as quantified using the 12-item World Health Organization Disability Assessment Schedule II.

Results Of 653 individuals referred to this study, 221 met the inclusion criteria and were randomized to receive PST or ST. Both PST and ST led to comparable improvement in disability in the first 6 weeks of treatment, but a more prominent reduction was noted in PST participants at weeks 9 and 12. The difference between PST and ST was greater in patients with greater cognitive impairment and more previous episodes. Reduction in disability paralleled reduction in depressive symptoms. The therapeutic advantage of PST over ST in reducing depression was, in part, due to greater reduction in disability by PST. Although disability increased during the 24 weeks after the end of treatment, the advantage of PST over ST was retained.

Conclusions These results suggest that PST is more effective than ST in reducing disability in older patients with major depression and executive dysfunction, and its benefits were retained after the end of treatment. The clinical value of this finding is that PST may be a treatment alternative in an older patient population likely to be resistant to pharmacotherapy.

doi:10.1001/archgenpsychiatry.2010.177

INFLAMMATION, SANITATION, AND CONSTERNATION

Charles L. Raison, MD & Colleagues - Arch Gen Psychiatry. 2010

Context: Inflammation is increasingly recognized as contributing to the pathogenesis of major depressive disorder (MDD), even in individuals who are otherwise medically healthy. Most studies in search of sources for this increased inflammation have focused on factors such as psychosocial stress and obesity that are known to activate inflammatory processes and increase the risk for depression. However, MDD may be so prevalent in the modern world not just because proinflammatory factors are widespread, but also because we have lost contact with previously available sources of anti-inflammatory, immunoregulatory signaling.

Objective: To examine evidence that disruptions in coevolved relationships with a variety of tolerogenic microorganisms that were previously ubiquitous in soil, food, and the gut, but that are largely missing from industrialized societies, may contribute to increasing rates of MDD in the modern world.

Data Sources: Relevant studies were identified using PubMed and Ovid MEDLINE.

Study Selection: Included were laboratory animal and human studies relevant to immune functioning, the hygiene hypothesis, and major depressive disorder identified via PubMed and Ovid MEDLINE searches.

Data Extraction: Studies were reviewed by all authors, and data considered to be potentially relevant to the contribution of hygiene-related immune variables to major depressive disorder were extracted.

Data Synthesis: Significant data suggest that a variety of microorganisms (frequently referred to as the "old friends") were tasked by coevolutionary processes with training the human immune system to tolerate a wide array of nonthreatening but potentially proinflammatory stimuli. Lacking such immune training, vulnerable individuals in the modern world are at significantly increased risk of mounting inappropriate inflammatory attacks on harmless environmental antigens (leading to asthma), benign food contents and commensals in the gut (leading to inflammatory bowel disease), or self-antigens (leading to any of a host of autoimmune diseases). Loss of exposure to the old friends may promote MDD by increasing background levels of depressogenic cytokines and may predispose vulnerable individuals in industrialized societies to mount inappropriately aggressive inflammatory responses to psychosocial stressors, again leading to increased rates of depression.

Conclusion: Measured exposure to the old friends or their antigens may offer promise for the prevention and treatment of MDD in modern industrialized societies.

http://archpsyc.ama-assn.org/cgi/content/abstract/67/12/1211?ct

COMPARATIVE BENEFITS AND HARMS OF SECOND-GENERATION ANTIDEPRESSANTS FOR TREATING MAJOR DEPRESSIVE DISORDER AN UPDATED META-ANALYSIS

Gerald Gartlehner, MD, MPH & Others - Ann Intern Med www. Annals.org

Abstract

Background second-generation antidepressants dominate the management of major depressive disorder (MDD), but evidence on the comparative benefits and harms of these agents is contradictory.

Purpose: To compare the benefits and harms of second from Pubmed, Embase, the Cochrane Library, PsycINFO, and international Pharmaceutical Abstracts from 1980 to August 2011 and reference lists of pertinent review articles and gray literature.

Study selection: 2 independent reviewers identified randomized trials of at least 6 weeks duration to evaluate efficacy and observational studies with at least 1000 participants to assess harm.

Data Extraction: Reviewers abstracted data about study design and conduct, participants, and interventions and outcomes and rated study quality. A senior reviewer checked and confirmed extracted data and quality ratings.

Data Synthesis: Meta-analyses and mixed-treatment comparisons of response to treatment and weighted mean differences were conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy of effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups bases on age, sex, ethnicity, or comorbid conditions, individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.

Limitations: Most trials were conducted in highly selected populations. Publication bias might affect the estimates of some comparisons. Mixed-treatment comparisons cannot conclusively exclude differences in efficacy. Evidence within subgroups was limited.

Conclusion: Current evidence dose not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. Differences in onset of action and adverse events may be considered when choosing a medication.

A RANDOMIZED TRIAL EXAMINING THE EFFECTIVENESS OF SWITCHING FROM OLANZAPINE, QUETIAPINE, OR RISPERIDONE TO ARIPIPRAZOLE TO REDUCE METABOLIC RISK: COMPARISON OF ANTIPSYCHOTICS FOR METABOLIC PROBLEMS (CAMP)

Stroup TS et al.. Am J Psychiatry 2011 Sep

Atypical antipsychotic medications are clinically effective, but often induce metabolic problems and weight gain. To assess the safety and effectiveness of switching antipsychotics to reverse these adverse effects, investigators conducted a multisite, NIH- and industry-funded, randomized, controlled, 24-week study.

The 215 clinically stable patients with schizophrenia or schizoaffective disorder had moderately increased cardiovascular risk, measured by metabolic indicators and elevated body-mass index (BMI), and were taking olanzapine (average dose, 18.5 mg/day), quetiapine (average, 502 mg/day), or risperidone (average, 4.1 mg/day). The study protocol involved staying on the current medication or switching to manufacturer-supplied aripiprazole in a gradual, 4-week cross-taper (mean dose during study, 16.9 mg/day). All patients received a behavioral intervention directed at diet and exercise; none took statins or weight-loss medications.

At 24 weeks, compared with controls, switchers to aripiprazole showed significantly greater decreases in non-HDL cholesterol (by 9.4 mg/dL), weight (by 2.9 kg), and BMI (by 1.1) and significantly improved trigylceride levels (difference of 32.7 mg/dL). The two groups showed no differences in symptom scores or treatment failures. However, significantly more switchers than controls stopped the protocol-specified treatment prematurely (47.7% vs. 27.4%). More switchers than controls reported insomnia and serious adverse effects.

Comment: The authors consider this degree of weight loss to be clinically significant and note that the decrease in non-HDL cholesterol is only slightly less than the decrease (10 mg/dL) associated with reduced risk for cardiovascular morbidity in a major bypass-angioplasty study. However, the treatment discontinuation rate and adverse effects in patients switched to aripiprazole are concerning. Switching patients to less metabolically problematic antipsychotics seems to be a worthwhile strategy, but requires careful monitoring and attention to the emergence of potentially disruptive adverse effects.

COMPARATIVE EFFICACY AND ACCEPTABILITY OF ANTIMANIC DRUGS IN ACUTE MANIA: A MULTIPLE-TREATMENTS META-ANALYSIS

Cipriani A et al - Lancet 2011 Aug 17

Both antipsychotic and mood-stabilizing medications have antimanic efficacy. In this meta-analysis, researchers examined the relative effectiveness of 14 antipsychotics and mood stabilizers by computing direct and indirect effect sizes and odds ratios. All drugs had at least one direct placebo-controlled comparison; most had at least three direct comparisons with other drugs. The researchers computed dichotomous outcomes from change scores at 3 weeks on the Young Mania Rating Scale and used study dropout rates to track tolerability.

On the primary efficacy outcome, only gabapentin and topiramate failed to beat placebo. In drug-drug comparisons, haloperidol fared the best; it was significantly more effective than all other treatments. Risperidone and olanzapine were the next most effective agents and were superior to valproate, ziprasidone, topiramate, lamotrigine, and gabapentin. On the primary tolerability outcome, risperidone, olanzapine, and quetiapine were best tolerated. **The best drugs, by their rank on a measure combining effectiveness and tolerability, were risperidone, olanzapine, haloperidol, quetiapine, and carbamazepine.**

Comment: This study is the first to comprehensively compute relative effectiveness and tolerability of multiple antimanic drugs. However, any suggestion that these results should inform bipolar treatment guidelines is overly simplistic and incomplete, because treatment of acute mania is only a tiny part of the overall treatment for bipolar illness. Achieving the vital objectives of preventing recurrences, reducing cycling, and addressing depression requires mood stabilizers and, sometimes, atypical antipsychotics. Editorialists note both these points and the fact that some dropouts were due to lack of efficacy, compromising dropout rates as a proxy for tolerability.

All antipsychotics and most benzodiazepines are effective for mania and generally have a more rapid onset of action than mood stabilizers like lithium because they are more sedating. Evidence supporting a true mood-stabilizing effect of antipsychotics as a drug class in maintenance therapy is not particularly robust (except for quetiapine). Thus, standard care should still involve consideration of one of the well-studied mood stabilizers such as lithium, carbamazepine, and valproate and the withdrawal of the antipsychotic, the adverse effects of which are far from benign.

(http://dx.doi.org/10.1016/S0140-6736(11)60873-8)

MAJOR DEPRESSION DURING AND AFTER THE MENOPAUSAL TRANSITION: STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

Bromberger JT et al. Psychol Med 2011 Feb 9

Menopause is thought to increase the risk for depression. However, studies have had conflicting results and methodological flaws, such as measuring depressive symptoms rather than major depression, not controlling for past episodes, not following women prospectively through the menopausal transition, and not extending follow-up into postmenopause. In this 10-year study, researchers examined the development of major depressive episodes through menopause in 221 premenopausal women who were participating in a longitudinal study of health in menopause and aging (144 whites; 77 blacks; age range at study entry, 42-52).

Participants had at least one visit in perimenopause, and 131 had at least one visit in postmenopause. By year 10, 30% of whites and 34% of blacks had at least one major depressive episode. Higher rates of major depression were associated independently with history of major depression, psychotropic medication use, high body-mass index, and upsetting life events (but not with frequent vasomotor symptoms or reproductive hormone levels). Even after adjustment for significant factors, major depression was two to four times more likely during perimenopause and postmenopause than premenopause. Depression was more common in the first 2 years after menopause (but not later) than in perimenopause.

Comment: This carefully done, long-term, prospective, cohort study demonstrates increased risk for major depression during the menopausal transition, especially within the first 2 years after menopause. Other factors (e.g., history of depression, life events) that increase risk at other stages of life also independently increase the risk. Given this relatively small study sample, further studies are needed to determine definitively whether frequent or severe vasomotor symptoms or hormone levels contribute to risk. Clinicians should view the menopausal transition and early postmenopause as a high-risk time for major depressive episodes and consider antidepressants and/or psychotherapy, which remain the mainstay of treatment, given conflicting data about the benefit of hormonal interventions.

http://psychiatry.jwatch.org/cgi/content/full/2011/321/1

اور کہا: عفیفہ پاک دامن کو کہتے ہیں۔

چونکہ فطرتاً آپ اندر سے پاک دامنی کو پسند کرتی ہیں، میری بھانجی کا نام بھی عفیفہ ہے۔

سوال: اس کے بعد کیا ہوا؟

جواب: میں نے بہنوئی کو فون کیا اور اس کو بتایا۔ وہ بہت خوش ہوئی۔ اس کے بعد میں نے اخبار میں اشتہار دیا، گزٹ میں نام بدلوایا، اپنی ہائی اسکول اور انٹر ڈگریوں میں نام بدلوایا اور ہاکی سے ریٹائرمنٹ لے کر گھر پر تعلیم شروع کر دی۔

سوال: اب آپ کا کیا ارادہ ہے، آپ کی شادی کا کیا ہوا؟

جواب: میں نے آئی سی ایس (انڈین سول سروس) کی تیاری شروع کی ہے۔ میں نے ارادہ کر لیا ہے کہ میں ایک آئی سی ایس افسر بنوں گی اور برقع پوش آئی ایس آئی افسر بن کر اسلامی پردے کی عظمت لوگوں کو بتاؤں گی۔

سوال: آپ اس کے لئے مطالعہ کر رہی ہیں؟

جواب: میں نیٹ پر اسٹڈی کر رہی ہوں۔ میرے اللہ نے ہمیشہ میرے ساتھ یہ معاملہ کیا ہے کہ میں جو ارادہ کر لیتی ہوں، اسے پورا کر دیتے ہیں۔ جب کافر تھی تو پورا کرتے تھے، اب تو اسلام کی عظمت کے لئے میں نے ارادہ کیا ہے، اللہ ضرور پورا کریں گے۔ مجھے ایک ہزار فی صد امید ہے کہ میں پہلی بار میں ہی آئی سی ایس امتحانات پاس کر لوں گی۔

سوال: مگر آپ کے انٹرویو کا کیا ہوگا؟

جواب: برقع اور اسلام کے سارے مخالف بھی اگر انٹرویو لیں گے تو وہ میرے انتخاب کے لئے ان شاء اللہ مجبور ہو جائیں گے۔

سوال: گھر والوں کو آپ نے دعوت نہیں دی؟

جواب: ابھی دعا کر رہی ہوں، اور قریب کر رہی ہوں۔ کتاب ''ہمیں ہدایت کیسے ملی؟'' گھر والوں کو پڑھوائی۔ سب لوگ حیران رہ گئے، اور اللہ کا شکر ہے کہ ذہن بدل رہا ہے۔

سوال: کوئی پیغام آپ دیں گی؟

جواب: عورت کا بے پردہ ہونا اس کی حد درجہ توہین ہے۔ مرد خدا کے لئے، اپنے جھوٹے مطلب اور اپنا بوجھ عورتوں پر ڈالنے کے لئے ان کو بازاروں میں بے پردہ پھرا کر ان کی تحقیر و تذلیل نہ کریں اور عورتیں اپنے مقام اور اپنی عصمت و عفت کی حفاظت کے لئے اسلام کے پردے کے حکم کی قدر کریں۔

(بہ شکریہ ماہنامہ 'ارمغان'، ضلع مظفر نگر، یوپی، نومبر ۲۰۱۰ء)

میں ڈنر پر پہنچی، تو سعدیہ نے اپنے قبولِ اسلام کی روداد مجھے سنائی اور بتایا کہ میں نے شادی کے لئے اسلام قبول نہیں کیا بلکہ اپنی شرم اور اپنی عصمت کی عزت و حفاظت کے لئے اسلام قبول کیا ہے اور اسلام کے لیے شادی کی ہے۔ سعدیہ نہ صرف ایک مسلم خاتون تھی بلکہ اسلام کی بڑی داعیہ تھی۔ اس نے فون کر کے دو انگریز لڑکیوں کو اور ایک معمر خاتون کو بلایا، جو ان کے محلے میں رہتی تھیں، اور سعدیہ کی دعوت پر مسلمان ہو گئی تھیں۔ وہ مجھے سب سے زیادہ اسلام کے پردے کے حکم کی خیر و برکت بتاتی رہیں اور بہت اصرار کر کے مجھے برقع پہنا کر باہر جا کر آنے کو کہا۔ میں نے برقع پہنا۔ ڈنمارک کے بالکل مخالف ماحول میں، میں نے برقع پہن کا گلی میں چکر لگایا، مگر برقع میرے دل میں اُتر گیا۔ بیان نہیں کر سکتی کہ میں نے مذاق اُڑانے یا زیادہ سے زیادہ اُس کی خواہش کے لئے برقع پہنا تھا، مگر مجھے اپنا انسانی قد بہت بڑھا ہوا محسوس ہوا۔ اب مجھے اپنے کوچ کی بے شرمانہ شہوانی چنگیوں سے گھن بھی آ رہی تھی۔ میں نے برقع اُتارا اور سعدیہ کو بتایا کہ مجھے واقعی برقع پہن کر بہت اچھا لگا، مگر آج کے ماحول میں جب برقعے پر مغربی حکومتوں میں پابندی لگائی جا رہی ہے، برقع پہننا کیسے ممکن ہے، اور غیر مسلم کا برقع پہننا تو کسی طرح ممکن نہیں؟ وہ مجھے اسلام قبول کرنے کو کہتی رہیں اور بہت اصرار کرتی رہیں۔ میں نے معذرت کی کہ میں اس کے لئے تیار نہیں ہوں۔ ابھی مجھے دنیا کی نمبر ون ہاکی کی کھلاڑی بننا ہے، یوں میرے سارے ارمانوں پر پانی پھر جائے گا۔

سعدیہ نے کہا: ''مجھے آپ کو ہاکی کے میدان سے برقعے میں لانا ہے۔ میں نے اپنے اللہ سے دُعا بھی کی ہے اور بہت ضد کر کے دُعا کی ہے۔'' اس کے بعد ہم ۱۰ روز تک ڈنمارک میں رہے۔ وہ مجھے فون کرتی رہی، دو بار ہوٹل میں ملنے آئی، اور مجھے اسلام پر کتابیں دے کر گئی۔

سوال: آپ نے وہ کتابیں پڑھیں؟

جواب: کہیں کہیں سے دیکھیں۔

سوال: اس کے بعد اسلام میں آنے کا کیا ذریعہ بنا؟

جواب: میں بھارت واپس آئی۔ ہمارے یہاں نریلا کے پاس گاؤں کی ایک لڑکی (جس کے والد ۱۹۷۴ء میں ہندو ہو گئے تھے، اور بعد میں آپ کے والد مولانا کلیم اللہ کے ہاتھوں مسلمان ہو گئے تھے، ان کے مرید بھی تھے اور حج بھی کر آئے تھے) ہاکی کھیلتی تھی۔ وہ دلی اسٹیٹ کی ہاکی ٹیم میں تھی اور بھارت کی طرف سے منتخب ہونے کے بعد روس میں کھیلنے جانے والی تھی۔ وہ مشورے اور کھیل کے انداز میں رہنمائی کے لئے میرے پاس آئی۔ میں نے اس سے ڈنمارک کی مشہور کھلاڑی برٹنی کا ذکر کیا۔ اس نے اپنے والد صاحب کو ساری بات بتائی۔ وہ اپنی لڑکی کے ساتھ مجھ سے ملنے آئے، اور مجھے حضرت کی کتاب ''آپ کی امانت'' اور ''اسلام ایک پریچے'' دی۔ ''آپ کی امانت'' چھوٹی سی کتاب تھی مگر برقعے نے میرے دل میں جگہ بنائی تھی۔ اس کتاب نے برقع کے حکم کو میرے دل میں بٹھا دیا۔ میں نے حضرت صاحب سے ملنے کی خواہش ظاہر کی۔ دوسرے روز حضرت کا پنجاب کا سفر تھا۔ اللہ کا کرنا کہ بہال گڑھ ایک صاحب کے یہاں ہائی وے پر ملاقات طے ہو گئی اور حضرت نے ۱۰، ۱۵ منٹ مجھ سے بات کر کے کلمہ پڑھنے کو کہا، اور انہوں نے بتایا کہ میرا دل یہ کہتا ہے کہ برٹنی نے اپنے اللہ سے آپ کو برقعے میں لانے کی بات منوائی ہے۔

بہر حال میں نے کلمہ پڑھا اور حضرت نے میرا نام عفیفہ رکھا،

جواب: ہاں، مگر فیصلہ کا حق مجھے تھا۔ میں نے فیصلہ کیا اور میں نے اپنے اللہ کا حکم سمجھ کر کیا، اب اللہ کے حکم کے آگے کے بندوں کی چاہت کیسے ٹھیر سکتی ہے۔

سوال: آپ کے اسلام میں آنے کا ذریعہ کیا چیز بنی؟

جواب: میں ہریانہ کے اس علاقے کی رہنے والی ہوں جہاں کسی ہندو کا مسلمان ہونا تو دور کی بات ہے، الٹا کتنے مسلمان ہیں جو ہندو بنے ہوئے ہیں۔ خود ہمارے گاؤں میں تیلیوں کے بیسیوں گھر ہیں جو ہندو ہو گئے ہیں، مندر جاتے ہیں، ہولی دیوالی مناتے ہیں۔ لیکن مجھے اسلام کی طرف وہاں جا کر رغبت ہوئی جہاں جا کر خود مسلمان اسلام سے آزاد ہو جاتے ہیں۔

سوال: کہاں اور کس طرح؟ ذرا بتائیں؟

جواب: میں ہاکی کھیلتی تھی تو بالکل آزاد ماحول میں رہتی تھی۔ آدھے سے کم کپڑوں میں ہندوستانی روایات کا خیال بھی ختم ہو گیا تھا۔ ہمارے اکثر کوچ مرد رہے۔ مرد ٹیم کے ساتھ ساتھ رہتے ہیں۔ ایک دوسرے سے ملتے ہیں۔ ٹیم میں ایسی بھی لڑکیاں تھیں جو رات گزارنے بلکہ خواہشات پوری کرنے میں ذرہ برابر کوئی جھجک محسوس نہیں کرتی تھیں۔ میرے اللہ کا کرم تھا کہ مجھے اس نے اس حد تک نہ جانے دیا۔ گول کے بعد اور میچ جیت کر مردوں عورتوں کا گلے لگ جانا، چمٹ جانا تو کوئی بات ہی نہیں تھی۔ میری ٹیم کے کوچ نے کئی دفعہ بے تکلفی میں میرے کسی شاٹ پر ٹانگوں یا کمر میں چٹکیاں بھریں۔ میں نے اس پر نوٹس لیا اور ان کو وارننگ دی، مگر ٹیم کی ساتھی لڑکیوں نے مجھے بُرا بھلا کہا کہ اتنی سی بات کو دوسری طرح لے رہی ہو، مگر میرے ضمیر پر بہت چوٹ لگی۔

ہماری ٹیم ایک ٹورنامنٹ کھیلنے ڈنمارک گئی۔ وہاں مجھے معلوم ہوا کہ ڈنمارک کی ٹیم کی سنٹر فارورڈ کھلاڑی نے ایک پاکستانی لڑکے سے شادی کر کے اسلام قبول کر لیا ہے، اور ہاکی کھیلنا بھی چھوڑ دیا ہے۔ لوگوں میں یہ بات مشہور تھی کہ اس نے شادی کے لئے اس لڑکے کی محبت میں اسلام قبول کیا ہے۔ مجھے یہ بات عجیب سی لگی۔ ہم جس ہوٹل میں رہتے تھے، اس کے قریب ایک پارک تھا، اس پارک سے ملا ہوا ان کا مکان تھا۔ میں صبح کو اس پارک میں سیر کر رہی تھی کہ ڈنمارک کی ایک کھلاڑی نے مجھے بتایا: وہ سامنے برٹنی کا گھر ہے جو ڈنمارک کی ہاکی کی مشہور کھلاڑی رہی ہے۔ اس نے اپنا نام اب سعدیہ رکھ لیا ہے اور گھر میں رہنے لگی ہے، مجھے اس سے ملنے کا شوق ہوا۔ میں ایک ساتھی کھلاڑی کے ساتھ اس کے گھر گئی۔ وہ اپنے شوہر کے ساتھ کہیں جانے والی تھی، پورے برقعے میں ملبوس۔ میں دیکھ کر حیرت زدہ رہ گئی اور ہم دونوں ہنسنے لگیں۔ میں نے اپنا تعارف کرایا تو وہ مجھے پہنچانتی تھی۔ وہ بولی میں نے تمہیں کھیلتے دیکھا ہے۔ سعدیہ نے کہا: ''ہمارے ایک سسرالی عزیز کا انتقال ہو گیا ہے، مجھے وہاں جانا ہے، ورنہ میں آپ کے ساتھ کچھ باتیں کرتی۔ میں تمہارے کھیلنے کے انداز سے بہت متاثر رہی ہوں۔ ہاکی کا کھیل عورتوں کی فطرت سے میل نہیں کھاتا۔ میرا دل چاہتا ہے کہ تمہاری صلاحیتیں فطرت سے رچاؤ رکھنے والے کاموں میں لگیں۔ میں تم سے ہاکی چھڑوانا چاہتی ہوں۔'' میں نے کہا: ''آپ میرے کھیل کے انداز سے متاثر ہیں اور مجھ سے کھیل چھڑوانا چاہتی ہیں، جب کہ میں تو آپ کا ہاکی چھوڑنا سن کر آپ سے ملنے آئی ہوں کہ ایسی مشہور کھلاڑی ہو کر آپ نے کیوں ہاکی چھوڑ دی؟ میں آپ کو میدان میں لانا چاہتی ہوں۔'' سعدیہ نے کہا: ''اچھا آج رات کو میرے ساتھ کھانے کی دعوت قبول کرو اور یہ طے ہو گیا۔

بھارت کی خاتون کھلاڑی کا قبولِ اسلام

قبول اسلام سے قبل عفیفہ ایک آزاد خیال ہندو لڑکی اور ہاکی کی کھلاڑی تھی۔ مگر جب اس نے اسلام کو فطرت کے قریب اور اپنے ضمیر کی آواز پایا تو اسے قبول کرلیا۔ قبولِ اسلام کے بعد معروف مبلغ محمد کلیم اللہ صدیقی کی بیٹی اسما نے ان سے انٹرویو کیا جو پیش ہے۔(ادارہ)

سوال: ہمیں بتایا گیا تھا کہ ہندوستان کی ایک ہاکی کھلاڑی آرہی ہیں تو ہم سوچ رہے تھے کہ آپ ہاکی کے لباس میں آئیں گی، مگر آپ ماشاءاللہ برقع میں ملبوس۔

جواب: الحمدللہ میں پچھلے دو ماہ سے شرعی پردے میں رہتی ہوں۔

سوال: ابھی آپ کے گھر میں تو کوئی مسلمان نہیں ہوا؟

جواب: جی، میرے گھر میں ابھی میرے علاوہ کوئی مسلمان نہیں ہے۔ اس کے باوجود میں الحمدللہ کوشش کرتی ہوں کہ میں اگرچہ گھر میں اکیلی مسلمان ہوں مگر میں آدھی مسلمان تو نہ ہوں، آدھی ادھر، آدھی اُدھر، یہ تو نہ ہونا چاہئے۔

سوال: اسلام قبول کرنے سے پہلے تو آپ کا نام پریتی تھا؟

جواب: حضرت کلیم صدیقی نے میرا نام عفیفہ، ابھی یعنی کچھ ماہ پہلے رکھا ہے۔

سوال: آزاد ماحول میں زندگی گزارنے کے بعد ایسے پردے میں رہنا آپ کو کیسا لگتا ہے؟

جواب: انسان اپنی فطرت سے کتنا ہی دور ہو جائے اور کتنے زمانے تک دور رہے جب بھی وہ اس کی طرف پلٹتا ہے تو وہ کبھی اجنبیت محسوس نہیں کرے گا۔ وہ ہمیشہ محسوس کرے گا کہ اپنے گھر لوٹ آیا۔ اللہ نے عورتوں کی فطرت مردوں سے بالکل الگ بنائی ہے۔ بنانے والے نے عورت کو چھپنے اور پردہ میں رہنے کے لئے بنایا۔ اسے سکون اور چین، لوگوں کی ہوس بھری نگاہ سے بچے رہنے میں ہی مل سکتا ہے۔ اسلام دین فطرت ہے، جس کے سارے حکم انسانی فطرت سے میل کھاتے ہیں، مردوں کے لئے مردوں کے فطرت کی بات، اور عورتوں کے لئے عورتوں کی فطرت کی بات۔

سوال: آپ کی عمر کتنی ہے؟

جواب: میری تاریخ پیدائش جنوری ۱۹۸۸ء ہے گویا ۲۲ سال۔

سوال: مسلمان ہوئے کتنے دن ہوئے؟

جواب: ساڑھے چھے مہینے کے قریب ہوئے ہیں۔

سوال: آپ کے گھر میں آپ کے اتنے بڑے فیصلے پر مخالفت نہیں ہوئی؟

جواب: ہوئی اور خوب ہوئی مگر سب جانتے ہیں کہ عجیب دیوانی لڑکی ہے، جو فیصلہ کرلیتی ہے پھر اس سے پیچھے نہیں ہٹتی۔ اس لئے شروع میں ذرا سختی ہوئی مگر جب اندازہ ہوگیا کہ میں دور تک جاسکتی ہوں تو سب موم ہوگئے۔

سوال: آپ ہاکی اب بھی کھیلتی ہیں؟

جواب: نہیں، اب میں نے ہاکی چھوڑ دی ہے۔

سوال: اسے تو گھر والوں نے بہت محسوس کیا ہوگا؟

Question on addiction, sex, psychiatry or the possession syndromes

First fold here

Second fold here

Remarks about the bulletin

Third fold here

Remarks about the bulletin

_____

_____

_____

_____

_____

_____

_____

_____

From

Stamp not necessary if mailed in Pakistan Postage will be paid by addressee

THE EDITOR

KARACHI PSYCHIATRIC HOSPITAL

B-1/14, NAZIMABAD # 3,

KARACHI, PAKISTAN-74600

Staple or stick with tape

کراچی نفسیاتی ہسپتال

1970 سے 2012

خدمت کے

42 سال۔۔۔

ہیڈ آفس: ناظم آباد B-1/14، ناظم آباد نمبر 3 کراچی
فون: 36708090 - 36616837

شمالی ناظم آباد: G/18 بلاک B، بمقابل ناظم آباد کراچی
فون: 36646648 - 3664484

شعبہ خواتین: 4F-12/13، ناظم آباد نمبر 4 کراچی
فون: 36684503

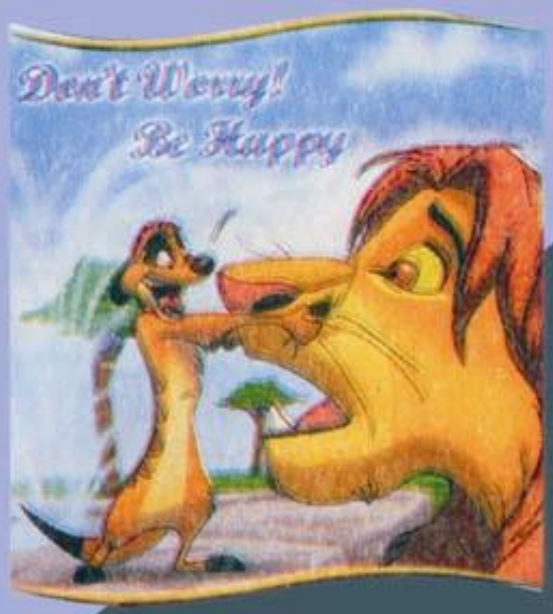
قائم آباد (لانڈھی): ایسوسی ایٹڈ سائیکاٹرک سوسائٹی انسٹیٹیوٹ کراچی
فون: 35013533 - 35016532

رمپا پاز و، کراچی نفسیات ہسپتال، رمپا پاز و ایم اے جناح روڈ
فون: 32720414 - 32721504

حیدر آباد کراچی نفسیاتی و نیورو ہسپتال B-81 بلاک A لطیف آباد نمبر 4
فون: 3812534

منتظم اعلیٰ: ڈاکٹر سید مبین اختر (ایم. بی. بی. ایس، سند یافتہ امریکہ)

111-760-760 www.kPh.org.Pk



Produces Tranquility

So A Great Companion

The Alprazolam
a world accepted
swift & safe
Tranquilizer for....

- Anxiety disorder
- Panic disorder
- Depression
- Social Phobia
- Pre-menstrual syndrome

Mazolam®

Alprazolam

Tablets 0.25 mg, 0.5 mg & 1 mg

munawar - pharma
(PVT) Ltd. Lahore
Ethical Marketing Division
224-A, First Floor, New Muslim Town, Lahore
Tel: 5841326-27 Fax: 5841328
E-mail: mpharm@wol.net.pk
Factory: 31, km, Ferozepur Road, Lahore,
ph: 5935073-4 Fax: 5935072

ISO 9001:2000 CERTIFIED
SGS