CHIEF EDITOR DR. SYED MUBIN AKHTAR

KARACHI PSYCHIATRIC HOSPITAL

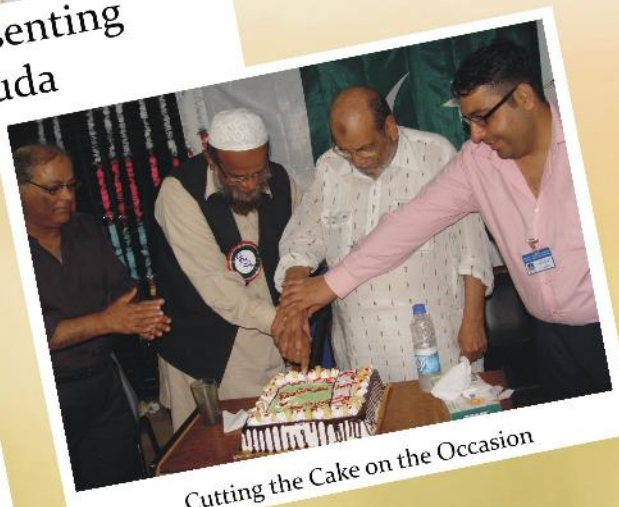
BULLETIN SEPTEMBER-2014

Dr. Syed Mubin Akhtar & Ameer J.I. Sindh Dr. Meraj ul Huda Siddiqui on independence day in K.P.H.

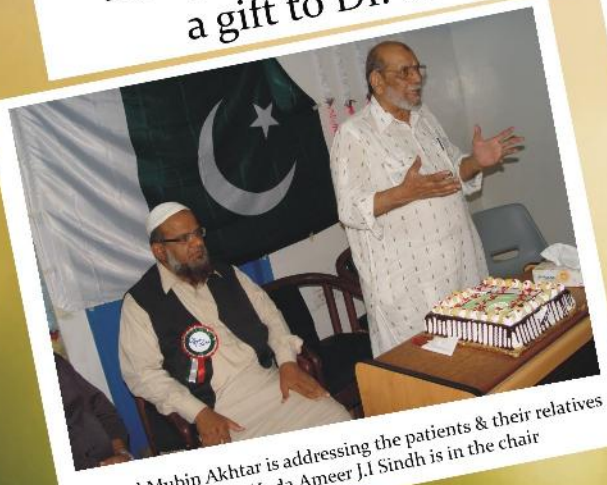
Hoisting the national flag on independence day by Dr. Syed Mubin Akhtar (MD-Karachi Psychiatric Hospital) & Chief Patron Tehreek Nifaz Urdu, Hakeem Mohammad Mujahid Barkati, & Ex MNA Laeeq Ahmed also participated

Happy Dale School held a Programe on independence day. Dr. Syed Mubin Akhtar Patron of the school addressing the students & teachers. Also present principal of the school M.S. Sagheer Fatima, Ms. Mehjabeen Akhtar DMD of Karachi Hospital, Syed Razi Hasan Nazim J.I. Naz# 4, & Mr. Umer Tawab, Deputy nazim

Dr. Syed Mubin Akhtar presenting a gift to Dr. Meraj ul Huda



Cutting the Cake on the Occasion



Dr. Syed Mubin Akhtar is addressing the patients & their relatives
Dr. Meraj ul Huda,Ameer J.I Sindh is in the chair

Female ward: DMD of Karachi Hospital Ms. Mehjabeen Akhtar presenting a gift to chief guest Dr. Fouzia

Cake cutting for the Celebration

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Vascular Psychiatry: A New Specialty?

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By David Hsu, MD [2]

Vascular surgeons, internists, and neurologists all exist—but why aren't there any vascular psychiatrists? There certainly is a need.

Vascular surgeons, internists, and neurologists all exist—but why aren't there any vascular psychiatrists? There certainly is a need.

Cardiovascular syndromes yield the highest morbidity and mortality of all diseases.[1] In daily practice, psychiatrists commonly encounter vascular syndromes, such as vascular depression,[2] vascular cognitive impairment,[3] and depression in heart disease.[4] Surgeons, internists, and neurologists can obtain subspecialty training in vascular disorders, but at this time, psychiatrists who are interested in this area are encouraged to pursue either psychosomatic medicine or geriatric psychiatry fellowships. Many psychiatrists who publish in vascular psychiatry are in one of those subspecialties. Therefore, vascular psychiatry at this time could be considered a sub-subspecialty.

Imagine a psychiatrist who is hubbed in a cardiovascular center clinic with cardiologists and vascular surgeons and who provides consultation on psychopharmacology or preoperative assessment. Or a psychiatrist who rounds in the cardiac ICU to evaluate depression, delirium, and dementia. Or a psychiatrist who rounds with the stroke team to evaluate cognitive impairment and provide psychotropic recommendations. These examples serve as innovative ways to collaborate and integrate care. Comorbidity of psychiatric syndromes, such as depression, and vascular diseases has already been firmly established. This has led to joint consensus guidelines from the American Heart Association, American Stroke Association, American Psychiatric Association, American Academy of Neurology, and the Alzheimer's Association.[3,4] There is no other area of medicine that has this high degree of collaboration.

Last year, the Royal College of Psychiatrists held a conference titled "Vascular psychiatry: the interface between vascular disease and mental disorders, and its clinical relevance."[5] Certainly, a similar conference could be held in the US. The specialty most closely related to vascular psychiatry at this time is probably vascular neurology,[6] and it is already part of the American Board of Psychiatry and Neurology. On their Web site, it states that vascular neurology is a "subspecialty that involves the evaluation, prevention, treatment, and recovery from vascular diseases of the nervous system."[6] Just substitute "the mind" for "the nervous system," and vascular psychiatry would be defined.

If a training fellowship for vascular psychiatry were to begin, I imagine that it would definitely have to be interdisciplinary. A central educational goal of a true "collaborative" fellowship would be to work with psychiatrists, cardiologists, neurologists, and surgeons. The fellow would be expected to go to didactics and rounds for all of these specialties and provide consultation on anything related to vascular psychiatry. Research would be cross-disciplinary, and grants could help to establish centers of excellence for vascular psychiatry, just like for geriatric psychiatry or depression. Interestingly, if a Society for Vascular Psychiatry were to be established, the initials would be "SVP," which also stands for "systemic venous pressure."

منتظم اعلیٰ کراچی نفسیاتی ہسپتال ڈاکٹر سید مبین اختر 14 اگست کے موقع پر تعلیمی نظام کو بہتر بنانے کیلئے گود لئے گئے سرکاری اسکول کی انتظامیہ اور بچوں سے خطاب کر رہے ہیں۔

Life Stress Reduces a Man's Sperm Quality

Mark L. Fuerst [2]
News [3] | June 10, 2014 | Anxiety [4]
By Mark L. Fuerst [2]

Men who feel stressed are more likely to have lower concentrations of sperm in their ejaculate and impaired sperm quality, which could be associated with fertility problems, according to a new study.

Men who feel stressed are more likely to have lower concentrations of sperm in their ejaculate and impaired sperm quality, which could be associated with fertility problems, according to a new study.

"Our study is the first to evaluate associations between work-related stress, stressful life events, and perceived stress and semen quality. We found that perceived stress and stressful life events, but not work-related stress, were associated with semen quality," lead author Pam Factor-Litvak, PhD, Associate Professor of Epidemiology at the Columbia University Mailman School of Public Health in New York, told ConsultantLive.

The cross-sectional study included 193 men, aged 38 to 49 years, who provided semen samples, as well as information on their stressors, both objective and subjective. Objective measures of stress included reports of life events that are known to cause stress; subjective measures of stress included reports of how the men felt. Stress related to both life and work was evaluated.

After taking into account reproductive health history and fertility concerns, Dr Factor-Litvak and colleagues found an association between life stress and semen quality. Although work stress did not seem to be linked with semen, they did find that job strain is associated with decreased testosterone, which could then affect reproductive health.

"We found an inverse association between perceived stress score and sperm concentration, motility, and morphology in covariate-adjusted linear regression analyses," Dr Factor-Litvak said. "Men who experienced 2 or more stressful life events in the past year compared with no stressful events had a lower percentage of motile sperm and a lower percentage of morphologically normal sperm but a similar sperm concentration."

The researchers were able to examine whether neuroendocrine disruption, via testosterone or follicle stimulating hormone, was responsible for at least part of the association, and it was not. "However, these analyses were only exploratory, so we cannot say for sure that this is not one of the mechanisms," said Dr Factor-Litvak.

Other proposed mechanisms include the stress-related production of seminal plasma reactive oxidative species, resulting in oxidative stress. "In other studies, oxidative stress is associated with semen quality and fertility," she noted. "Clearly, more research is needed to identify all the mechanisms. There are likely to be more than one."

The data did reveal an expected relationship between testosterone levels and semen quality but did not find associations between most stress measures and testosterone levels. "However, our analyses here were only exploratory," Dr Factor-Litvak said. "Other studies have found associations between stress and testosterone, likely due to the effect stress has on neuroendocrine factors that influence sperm production. Those investigators posit that stress leads to increases in glucocorticoids, which leads to decreased testosterone production from Leydig cells, which are responsible for sperm production."

The researchers did not study the effects of stress reduction, but "good health habits, including regular exercise and good dietary patterns, are advisable for all," Dr Factor-Litvak said.

She noted that "this study found associations between life stress and unemployment, and semen quality. It is only one study, and more research is clearly needed to confirm the association and to explore the potential mechanisms."

The researchers presented their results online on May 22, 2014 in *Fertility and Sterility.*

Skin Rashes with Antiepileptic Drugs

Allan S. Brett, MD reviewing *Hirsch LJ et al. Neurology 2008 Nov 4.*

Of 1875 outpatients with epilepsy, 14% developed rashes that were thought to be caused by at least one antiepileptic drug; 4% developed rashes with two or more drugs.

Antiepileptic drugs are associated with high rates of skin rash, and cross-sensitivity among antiepileptic drugs is not uncommon. In this retrospective chart-review study from Columbia University, researchers determined the incidence of cross-sensitivity among pairs of antiepileptic drugs.

Of 1875 outpatients (age, ≥12) with epilepsy, 14% developed rashes that were thought to be caused by at least one antiepileptic drug; 4% developed rashes with two or more drugs. Of 81 patients with phenytoin rashes who were prescribed carbamazepine, 42% also developed rashes with carbamazepine. Of 59 patients with carbamazepine rashes who were prescribed phenytoin, 58% also developed rashes with phenytoin. For the other four most common rash-causing drugs in this cohort (lamotrigine, oxcarbazepine, phenobarbital, and zonisamide), the absolute number of patients exposed to specific drug pairs was generally small, and incidences of cross-reactive rashes ranged from 0% to 70%. Incidence of antiepileptic drug rash was much higher among patients who reported previous allergic reactions to non-antiepileptic drugs than among patients who reported no other drug allergies.

- See more at: http://www.jwatch.org/jw200811200000003/2008/11/20/skin-rashes-with-antiepileptic-drugs#sthash.7Ozx2DU1.dpuf

Suicide and the Nightmarish Life

Gregory Fricchione, MD reviewing *Sjöström N et al. Sleep 2007 Jan 1.*

This study reveals that nightmares are associated with suicidality and that sleep dysfunction is prevalent among people who attempt suicide.

These authors assessed the prevalence of nightmares among suicide attempters and tested the associations between specific sleep disturbances and suicidality.

Of 323 patients hospitalized after a suicide attempt, 165 (22% men; 25% with less than a high school education) underwent a structured clinical interview to assess Axis I psychiatric disorders. Sleep dysfunction was studied using the Uppsala Sleep Inventory. Symptom intensity was assessed using anxiety and depression subscales of the CPRS Self Rating Scale for Affective Syndromes. Suicidality was assessed with the Suicide Assessment Scale (SUAS).

Of the cohort, 89% reported sleep disturbances of some kind, and two thirds reported having nightmares. Having frequent nightmares was the only sleep variable associated with high suicidality. In a final multivariate model including all covariates and compared with participants without nightmares, those with nightmares had an odds ratio for having the highest versus the lowest SUAS score of 3.7 (95% confidence interval, 1.5–9.0; $P<0.005$).

The authors conclude that sleep disturbances are common among suicide attempters and that nightmares are intimately correlated with suicidality. They note that generalizability of the findings is limited by the high proportion of patients who did not complete the routine interviews, by selection bias in sex and educational level, and by the lack of a control group of nonsuicidal patients with psychiatric disorders.

Early Life Stress Linked with Epigenetic Changes in Children

Alain Joffe, MD, MPH, FAAP reviewing *Romens SE et al. Child Dev 2014 Jul 24.*

Children with a history of maltreatment had increased methylation of key portions of the glucocorticoid receptor gene.

Individuals exposed to extreme levels of early life stress are at increased risk for developing a range of mood and behavioral disorders. Investigators sought to determine if the association noted in animals between early life stress and methylation of the glucocorticoid receptor gene involved in the stress response is also found in children. They recruited 56 children (30 boys; age range, 11–14 years; 66% white); 18 had documented history of physical maltreatment in Child Protective Services records. DNA from blood leukocytes was examined for changes in the glucocorticoid receptor promoter gene *NR3C1*.

Maltreated children were similar in age, sex, and race/ethnicity to those without a history of maltreatment, but were from families with lower socioeconomic status (SES). Compared with children without a history of maltreatment, maltreated children had significantly more methylation at a number of sites in the *NR3C1* gene. This same pattern was observed in analysis restricted to SES-matched children with and without histories of maltreatment.

Mothers' Fear Is Transmitted to Offspring: An Animal Study

Barbara Geller, MD reviewing *Debiec J and Sullivan RM. Proc Natl Acad Sci U S A 2014 Jul 28.*

Infants exposed to mothers conditioned to fear a peppermint odor developed an aversion to the odor.

Intuitively, it seems unlikely that infants have sufficient cognitive capacity to incorporate a mother's fears from environmental cues. To test this possibility, researchers conducted fear-conditioning experiments in female rats and young pups.

Before breeding, rats either were or were not conditioned to a foot shock (unconditioned stimulus [US]) paired with peppermint odor (conditioned stimulus [CS]). At about age 1 week, pups and mothers were exposed or not exposed to the CS. CS-exposed pups of fear-conditioned mothers showed aversion to the peppermint odor, unlike CS-exposed pups of control mothers and nonexposed pups of fear-conditioned mothers. To test whether behaviors of fear-conditioned mothers might affect results, researchers tested aversion in pups exposed to surrogate mothers with or without fear conditioning or to the odor of fear-conditioned mothers; the biological odor and surrogate fear conditioning produced the same aversion in CS-exposed pups. Pups with CS aversion had elevated stress indicators, including increased corticosterone and postmortem elevated amygdala activity, which were prevented with corticosterone antagonists or amygdala inhibition.

A Genetic and Epigenetic Biomarker for Suicide?

Joel Yager, MD reviewing *Guintivano J et al. Am J Psychiatry 2014 Jul 30.*

In blood samples from several cohorts, a biomarker with genetic and epigenetic variation near *SKA2* on chromosome 17 predicted suicide and suicidal behaviors with 80% accuracy.

The search for biomarkers that accurately predict suicidal behaviors and suicide is a high priority. These researchers conducted a series of studies of a possible biomarker.

First, they performed preliminary DNA methylation studies on prefrontal cortical tissue from people who died by suicide or from other causes. In both neurons and glia in a subgroup of white, depressed suicide cases, researchers identified a promising epigenetic-genetic biomarker — a C for T allele substitution, which permits epigenetic DNA methylation — near the *SKA2* gene on chromosome 17. Compared with controls, people who died by suicide had lower *SKA2* expression and substantially higher rates of DNA methylation in the *SKA2* region. This finding was replicated with samples from two other brain banks. The polymorphism was associated with lower expression of glucocorticoid receptors, which is ultimately associated with diminished ability to suppress cortisol; in one cohort, lower suppression of cortisol was associated with epigenetic and genetic variations.

The researchers then measured the biomarker in peripheral blood from three samples of living subjects. Among those with high self-ratings of stress or anxiety, the presence of the biomarker increased the risk for suicidal ideation and, among those with suicidal ideation, increased the risk for suicide attempts. Although samples were small, researchers developed a model predicting suicidal ideation and attempts with an estimated overall 80% accuracy.

Even Moderate Alcohol Intake Is Associated with Atrial Fibrillation

Kirsten E. Fleischmann, MD, MPH reviewing *Larsson SC et al. J Am Coll Cardiol 2014 Jul 22. Conen D and Albert CM. J Am Coll Cardiol 2014 Jul 22.*

One to three drinks daily increased relative risk by roughly 10% to 20%.

Consuming large quantities of alcohol is linked to excess risk for atrial fibrillation (AF), but what about more moderate intake? To answer the question, Swedish researchers conducted a prospective cohort study and then performed a meta-analysis that included their study and six others.

In the Swedish study, relative risks for AF among participants whose weekly alcohol intakes were 1 to 6 drinks, 7 to 14 drinks, 15 to 21 drinks, and >21 drinks, were 1.01, 1.07, 1.14, and 1.39, respectively, compared with those who had <1 drink weekly. Results were similar even when binge drinkers (i.e., those who consumed ≥5 drinks on a single occasion) were excluded. In the meta-analysis of seven studies (>12,000 cases of AF), relative risks associated with daily alcohol intakes of 1, 2, 3, 4, and 5 drinks were 1.08, 1.17, 1.26, 1.36, and 1.47, respectively, compared with nondrinking.

Alcohol Consumption: The Less, the Better

Beat J. Meyer, MD reviewing *Holmes MV et al. BMJ 2014 Jul 10.*

A simple interpretation of a Mendelian randomization meta-analysis provides convincing evidence.

Observational studies suggest that light-to-moderate alcohol consumption may be protective against cardiovascular disease, but the findings could be due to residual confounding or selection bias. Can the lack of evidence from randomized trials be overcome by a genetic approach? Researchers in a large, international collaboration conducted a Mendelian randomization meta-analysis of associations between alcohol consumption and cardiovascular biomarkers and events. The meta-analysis covered 56 epidemiological studies with data on a single nucleotide polymorphism (SNP, rs1229984) in the alcohol dehydrogenase 1B gene (*ADH1B*), which encodes the ADH1B enzyme accounting for much of the ethanol metabolic pathway.

The rs1229984 variant, which has been linked to flushing after alcohol consumption, less alcohol consumption, and a lower risk for alcohol dependence, was used as a proxy of alcohol consumption. The meta-analysis covered more than 260,000 individuals of European descent, including 20,259 cases of coronary heart disease and 10,164 stroke events. Compared with GG homozygotes, carriers of the A allele consumed significantly fewer alcohol units weekly, were less likely to binge drink (odds ratio, 0.78), and were more likely to abstain (OR, 1.27). They also had lower systolic blood pressure (−0.88 mm Hg), interleukin-6 levels (−5.2%), and body-mass index.

Regarding the main clinical outcome, A-allele carriers had a significantly lower risk for coronary heart disease (OR, 0.90) across all categories of alcohol consumption (heterogeneity, P=0.83). As to secondary outcomes, the A allele was associated with lower risk for ischemic stroke (OR, 0.83), but not with risk for combined stroke subtypes.

Off-Label Use of Atypical Antipsychotics: Benefits Vary More Than Harms

Peter Roy-Byrne, MD reviewing *Maher AR et al. JAMA 2011 Sep 28.*

This drug class can be modestly effective depending on the drug and condition, but adverse events are uniformly problematic.

Various atypical antipsychotics have FDA indications for schizophrenia, bipolar illness, and depression but are increasingly used off-label for other conditions. These researchers examined the efficacy and safety of off-label uses in meta-analyses of controlled trials and large observational studies.

Strong evidence from 14 placebo-controlled trials indicated small effects of atypical antipsychotics for behavioral disturbances in dementia, with no difference among aripiprazole, olanzapine, and risperidone. Modest evidence from three placebo-controlled trials indicated small effects of quetiapine for generalized anxiety disorder. Modest evidence from three placebo-controlled studies showed large effects of risperidone augmentation of antidepressants in obsessive-compulsive disorder (OCD). Support for antipsychotic use was nonexistent in eating disorders and substance abuse and marginal in personality disorders and post-traumatic stress disorder (see JW Psychiatry Aug 2 2011). Various antipsychotics in older populations were associated with increased risk for death (number needed to harm [NNH], 87), stroke (risperidone: NNH, 53), extrapyramidal symptoms (EPS; olanzapine: NNH, 10), and urinary tract symptoms (NNH, 16–36). Problems in nonelderly populations included weight gain (olanzapine: NNH, 3), fatigue, akathisia, and EPS.

Vitamin D and Cognitive Decline

Jaime Toro, MD reviewing *Littlejohns TJ et al. Neurology 2014 Sep 2.*

Is vitamin D deficiency in elders a risk factor for dementia and Alzheimer disease?

Clear evidence supports a crucial role for vitamin D in neuronal function. Vitamin D and its metabolites mediate the synthesis of various neurotransmitters including acetylcholine, catecholamines, serotonin, and dopamine. Vitamin D also helps maintain neurite outgrowth and promote synaptic plasticity, influences neurotransmitter synthesis, protects against oxidative stress and mitochondrial dysfunction, reduces the proinflammatory response, and regulates ageing. Thus, a role for vitamin D in the pathogenesis of cognitive impairment and Alzheimer disease (AD) is plausible (*Neuropathol Appl Neurobiol* 2013; 39:458). To examine this association, researchers studied 1658 ambulatory adults (mean baseline age, 74) who were free from dementia, cardiovascular disease, and stroke who participated in the U.S. population-based Cardiovascular Health Study. Serum 25-hydroxyvitamin D (25[OH]D) concentrations were determined from blood samples taken in 1992 and 1993. Deficiency was defined as 25 nmol/L to <50 nmol/L, severe deficiency as <25 nmol/L. Follow-up for dementia and AD status was based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

During a mean follow-up of 5.6 years, 171 participants developed all-cause dementia, including 102 with AD. The risks for both all-cause dementia and AD were significantly higher in participants who were either 25(OH)D-deficient (53% and 69% higher risks, respectively) or severely deficient (125% and 122% higher risks, respectively). Adjustments, including removal of cases diagnosed in the first year, did not alter these associations.

Small-Bowel Mucosal Damage with Low-Dose Aspirin Therapy

David J. Bjorkman, MD, MSPH (HSA), SM (Epid.) reviewing *Endo H et al. Gastrointest Endosc 2014 May 13.*

Concomitant proton-pump inhibitor use doubled the risk for mucosal lesions.

Low-dose aspirin (75–325 mg per day) is associated with small-intestine damage. To assess the magnitude of this effect and associated risk factors, investigators in Japan prospectively collected data from 205 patients taking low-dose aspirin who were referred to one of five hospitals for video capsule endoscopy (VCE). All patients had previous negative upper gastrointestinal endoscopy and colonoscopy prior to entry into the study.

Of 198 patients included in the final analysis, 114 (57.6%) had at least one mucosal lesion detected by VCE. In multivariate analysis, only the use of proton-pump inhibitors (PPIs) and use of enteric-coated aspirin were associated with increased risk for mucosal lesions (odds ratios, 2.04 and 4.05, respectively).The authors conclude that PPI use increases the risk for mucosal breaks in the setting of low-dose aspirin therapy.

رہنما جماعت اسلامی معراج الہدیٰ صدیقی اور منتظم اعلیٰ کراچی نفسیاتی ہسپتال ڈاکٹر سید مبین اختر مرکزی شاخ میں مریضوں کے ساتھ 14 اگست جشن آزادی منا رہے ہیں۔

What Can the Media do for Your Practice?

Anthony G. Alessi, MD [2]

Blog [3] | July 18, 2014

By Anthony G. Alessi, MD [2]

Neurologists are often tapped by the media to explain complex conditions to a nonphysician audience. As part of a marketing strategy, offering your expertise to local media outlets helps them report accurately and burnishes your reputation.

The media—print, radio, television—can be a valuable tool for a neurology practice. Access to the media often provides a way of marketing a new service or level of expertise within a practice

When a healthcare practitioner serves as a source of information for the media it creates the perception of an honest, authoritative spokesperson. It gives a physician instant credibility. It is also a much better way to advertise your services than purchasing an ad.

Neurologists are particularly sought out by various media outlets to explain complex conditions involving the brain and peripheral nervous system. Many neurologic illnesses can result in severe disability, change in mentation, or death, all outcomes that are particularly important to the public.

Media contacts can best be established by partnering with a hospital or professional organization that has a public relations department. Being available to be interviewed on short notice is valuable to both a journalist working on a deadline and to organizations (eg, hospitals, local chapters of professional organizations) looking for someone to

represent them in the media. Professional societies like the American Academy of Neurology offer media training sessions.

To develop the media relations part of a marketing strategy, a neurologist should understand the importance of creating a concise, understandable message on the topic of interest to the press. This is often referred to as the “sound bite.”

Prior to an interview or when preparing a written communication, decide on three to five main points to develop that you want your audience to remember afterward and make sure you work them into the conversation or your written material. Writing them on an index card is helpful.

Here are some useful tips when preparing for a radio or television interview:

* **Practice.** Anticipate tough questions, practice the answers. Make sure you get your points into the discussion.

* **Prepare.** Familiarize yourself with the interviewer’s style. In the case of a panel discussion, learn about the other panelists. Watch or listen to the program in advance.

* **Attire.** Dress professionally.

* **Communication.** For the best clarity use a landline for telephone interviews that are being recorded.

* **Message.** Keep the message simple and direct by using terms that the public will understand.

Bottom line: If you deliver your message carefully and articulately, your work with the press can have a very positive impact on a neurology practice.

Borderline Personality Disorder and Bipolar Disorder—Distinguishing Features of Clinical Diagnosis and Treatment

Since the inclusion of the borderline personality disorder (BPD) diagnosis in DSM, there have been multiple efforts to recast the disorder as part of an Axis I illness category. While the initial focus was on the schizophrenia spectrum,[1] more recent authors have attempted to link BPD to mood disorders. There is considerable literature on the relationship between major depressive disorder (MDD) and BPD, and although the current understanding posits distinct disorders, overlapping biological underpinnings do exist.[2] Attention has now turned to bipolar disorder, with several vocal advocates who propose reclassifying BPD as bipolar spectrum disorder.[3,4] This article discusses the overlapping phenomenology of bipolar disorder and BPD and highlights distinguishing features of clinical diagnosis and treatment.

Prevalence

According to DSM-IV-TR, the prevalence of BPD is estimated at 2% of the general population, compared with 1% to 2% for bipolar disorder. Other estimates are closer to 5% for bipolar spectrum disorder.[5] Depending on the population studied, there are varying estimates of the co-occurrence of BPD and bipolar disorder. In a recent comprehensive review by Paris and colleagues,[6] the rate of bipolar I disorder in BPD patients ranged from 5.6% to 16.1%, with a median of 9.2%. The rate of bipolar II disorder was only slightly higher, 8% to 19%, with a median of 10.7%. The 2 studies with the strongest methodologies that used structured diagnostic interviews with adequate sample sizes and a 6- to 7-year follow-up showed a low rate of new onset of bipolar disorder in patients with BPD, with no difference from the comparison groups.[7,8] A recent study that used the large Collaborative Longitudinal Study of Personality Disorders (CLPS) database, however, showed an increased rate of bipolar I and II

disorders in patients with BPD compared with patients who had personality disorders other than BPD, including schizotypal, avoidant, and obsessive-compulsive personality disorders (19.4% and 7.9%, respectively). In addition, BPD patients had a higher rate of bipolar I and II disorder onset (8.2% for BPD vs 3.1% for the other personality disorders) over 4 years.[9] While these studies suggest a moderately increased risk for bipolar disorder in patients with BPD, it was not nearly as high as the risk for MDD or substance abuse.

The rate of BPD in patients with bipolar I disorder varies from 0.5% to 30%, with a median of 10.7%, while in patients with bipolar II disorder, the rates are 12% to 23%, with a median of 16%.[6] The relationship of BPD and cyclothymia has been examined in 1 study, and the results revealed exceptionally high comorbidity rates with BPD of 62%.[10] However, while elevated rates of comorbid personality disorders have been found in patients with bipolar disorder, no differences between rates of BPD and the other personality disorders studied have emerged.6 These findings suggest that while BPD and bipolar disorder can co-occur, in general, comorbidity is not common.

Diagnosis

Diagnosis of bipolar disorder or BPD can be difficult, because both can present with affective instability, irritability, and impulsivity. A comparison of DSM-IV-TR criteria is displayed in Table 1 and demonstrates considerable overlap.

The phenomenology of mania differs significantly from that of BPD. Factor analyses of manic symptoms have identified psychic and motor acceleration, psychosis, and irritability.[11,12] A factor analysis and subsequent replication study revealed 3 factors for BPD: disturbed relatedness, behavioral dysregulation, and affective dysregulation.[13,14] However, a number of recent studies have shown that the BPD factors correlate so highly with one another (with correlation coefficients of 0.92 to 0.98) that the factor analyses actually support a single overarching BPD construct.[15-17]

Recent studies that explored the overlap of BPD and bipolar disorder have outlined several parameters to distinguish the 2 diagnoses[9,18,19]:

• Quality of mood episodes
• Types of impulsivity
• Longitudinal course

Symptoms such as irritability and quality of depression have not proved helpful.

Mood episodes

While both disorders cause mood instability and affective reactivity, the phenomenologies of the mood episodes differ. In BPD, mood swings, usually of negative affect, are triggered by interpersonal stressors or perceived stressors, are transient, last from minutes to hours, and are highly dependent on the environment. In bipolar disorder, mood swings are more spontaneous and of longer duration, especially for bipolar I disorder, and there are more extended periods of elation. In addition, in bipolar disorder, acute episodes and symptom-free intervals occur, while in BPD, the affective instability is part of a characteristic pattern of emotional responding. Data suggest that these affective problems persist throughout the life course of the disorder and may be identified by parents of children with BPD as early as infancy.[20,21]

The mood swings of BPD and bipolar II disorder differ in emotion type as well. Individuals with BPD swing from euthymia to anger, and euthymia is infrequent, while bipolar II disorder affective shifts are from euthymia to elation.[22] Shifts triggered by interpersonal stressors in BPD, which often involve rejection or perceived abandonment, are less prevalent in bipolar disorder.[23] The differentiation of BPD and rapid cycling bipolar disorder remains problematic, as both disorders involve a high degree of affective instability, and the 2 entities are likely to have significant biological and possibly genetic overlap.[24] Findings from these 3 studies suggest that careful detailing of the duration of

mood episodes, qualitative emotional shifts, recurrent triggering events, and longitudinal patterns (episodic vs lasting) can help distinguish between BPD and bipolar disorder, although not rapid cycling forms of bipolar disorder.[22-24]

Impulsivity

Impulsivity is behavior that occurs without reflection, is inconsistent with context, and is seen in both BPD and bipolar disorder.[25] Differential patterns of impulsivity have been characterized for the depressive and manic phases of bipolar disorder with motor impulsivity (tendency to act on the spur of the moment) specific to mania and non-planning impulsivity (lack of sense of the future) specific to depression. Impulsivity in BPD is also characterized as non-planning.[26-28] These data support the premise that BPD may have more symptomatic overlap with the depressive pole of bipolar disorder than with the manic pole.

Similarly, BPD was distinguished from bipolar II disorder by the presence of hostility and differing patterns of impulsivity. Bipolar II disorder showed attentional impulsivity characterized by distractibility and inability to focus on a task, and BPD displayed non-planning impulsiveness. The highest rate of impulsivity was found in populations with comorbid BPD and bipolar II disorder, which suggests that this group may be at the highest risk for self-damaging behaviors.[28] This finding argues for the need to make both diagnoses when appropriate.

Clinically, impulsivity is believed to be more episodic in bipolar disorder than in BPD, although inter-episode impulsivity is seen in bipolar disorder when comorbid substance abuse complicates the clinical picture.[29] Impulsive acts such as suicidal behavior occur in both disorders, but in bipolar disorder these are predominantly found in the depressive phase, particularly in mixed depressive presentations, and they are related to hopelessness while in BPD, they are often a function of the inability to tolerate distress.[30-32]

Longitudinal course

Long-term outcome studies in bipolar disorder and BPD seem to challenge the traditional Axis I/Axis II dichotomy, in which mood disorders are widely thought of as episodic and treatable, whereas personality disorders are considered life-long and treatment refractory. Many cases of bipolar disorder assume a chronic course, with long-term morbidity and substantial inter-episode symptomatology, whereas multiyear follow-up studies of patients with BPD have found that most people eventually stop meeting threshold criteria for the disorder.[5,33,34] However, there appears to be a core subset of BPD symptoms, especially in the affective and interpersonal realms, that persist even after the more dramatic impulsive or demanding behaviors have subsided. There also appears to be a subset of remission-resistant BPD patients who continue to show poor judgment and high treatment utilization.[35,36]

Findings from prospective studies on the interactive effects of both disorders indicate that comorbid bipolar disorder had no effect on the clinical course of BPD with respect to functional outcome, remission rates, or number of hospitalizations or other treatment utilization except for mood-stabilizer medication.[9]

Treatment implications

Differentiating BPD from bipolar disorder has ramifications for treatment planning, both pharmacological and psychosocial.

Pharmacological treatment

While randomized clinical trials of patients with BPD have been performed using mood stabilizers, antidepressants, and typical and atypical antipsychotics, their effect sizes have not been particularly robust. This, coupled with small sample sizes, prompted the recent Cochrane review to state that there are "insufficient data" to support any recommendations for pharmacological treatment in BPD. The report concluded that medication effects in BPD are "unimpressive."[37] Despite this, although not empirically

validated, study findings suggest that polypharmacy for BPD is rampant, and it is not uncommon for patients with BPD to be treated with multiple agents.[38] This can result in significant iatrogenic morbidity that may outweigh the marginal clinical benefits. In contrast, pharmacological treatment in bipolar disorder is far more effective. Eleven drugs are FDA-approved for the treatment of bipolar disorder: 9 for mania/mixed phases, 2 for depressive phases, and 5 for maintenance therapy (several are approved for more than one phase of the illness).

Although similar medications are used for both BPD and bipolar disorder, the clinical effectiveness of the medications and target symptoms of the disorders differ. In bipolar I disorder patients, mood stabilizers are the first line of treatment. In BPD, randomized controlled trials of valproate and carbamazepine have targeted impulsivity and anger rather than affective instability, while a randomized controlled trial of lithium showed no benefit at all.[39-42] Similarly, randomized controlled trials of newer mood stabilizers such as topiramate and lamotrigine have been shown to target anger rather than affective instability.[43,44]

A positive clinical response has been found for antidepressants of several classes including monoamine oxidase inhibitors and SSRIs, for both the depressed phase of bipolar disorder and for BPD. The propensity of antidepressants to produce manic symptoms in patients with bipolar disorder is always a consideration despite controversy about the magnitude or clinical importance of the risk, but this does not seem to be the case for BPD. SSRIs in BPD appear to target anger and impulsivity, rather than mood symptoms; a similar finding was noted by Paris[19] in a study of atypical antipsychotics for both BPD and bipolar disorder.

The findings on medication treatment in patients with BPD suggest that an over-reliance on psychopharmacological strategies yields disappointing results. Medication efficacy is far more pronounced in patients with bipolar disorder.[33,45] The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a longitudinal study of 4107

persons with bipolar disorder that evaluated treatment effectiveness, has generated valuable data on head-to-head medication trials and will continue to provide insights into optimal treatment strategies for the various phases of bipolar disorder.[46]

Psychosocial interventions

Table 2 presents psychosocial treatments available to patients with bipolar disorder or BPD. Despite symptomatic overlap, the types of interventions differ by disorder.

In contrast to the meager efficacy of pharmacological treatment for BPD, psychosocial treatments have shown substantial promise and many psychotherapeutic interventions that focus on teaching emotion-regulation skills exist. These include:

• Dialectical behavior therapy[47]
• Systems training for emotional predictability and problem solving (STEPPS)[48]
• Schema-focused therapy[49]
• Mentalization-based treatment[50]
• Transference-focused psychotherapy[51]

Psychoeducation has been identified as an inte-gral component in the treatment of BPD, and it has been usefully extended to family members as well.[52,53]

In bipolar disorder, the value of psychosocial interventions is gaining recognition as an important adjuvant treatment. The therapeutic aims of psychosocial approaches for bipolar disorder include psychoeducation, stress management, and regularity in daily activitiesand biosocial rhythms.[54-57]

Case Vignette

John is a 50-year-old, white, never-married man who initially presented with irritability and depression. He denied any current or past suicidal or homicidal ideation but endorsed

a past history of “mood swings.” He had been given a diagnosis of bipolar II disorder 10 years earlier. John described his moods as never vacillating to periods of elation but rather as centered on feelings of hostility and anger. He had a 20-year history of heavy alcohol use and reported that he had completed a court-mandated alcohol rehabilitation program several years earlier.

Over the next few sessions, his preoccupation with his partner’s fidelity and whereabouts, his dependency on others, identity confusion, and impulsivity manifested themselves. He had rapid mood shifts in session, particularly when the discussion centered on his current romantic relationship of 5 months. Given the quality of his mood swings and associated symptoms, BPD was diagnosed and John was referred for medication management and dialectical behavior therapy.

As noted by Gunderson and colleagues,[9] and as exemplified by this case, persons with BPD often receive a diagnosis of bipolar spectrum disorder. The failure to appreciate the BPD diagnosis, whether from misdiagnosis or a hesitancy to offer a stigmatizing label, can affect treatment outcome. As previously discussed, the effects can range from overuse of medication and potential polypharmacy to an underappreciation of empirically validated psychological treatments of BPD.

Conclusion

BPD and bipolar disorder are both associated with significant levels of mortality and morbidity, and they present diagnostic challenges because of their phenotypic overlap. However, paying attention to the patient’s quality of mood shifts, types of impulsivity, and longitudinal course may aid in distinguishing between the 2 disorders. Accurate diagnosis is important because each disorder has a distinct medication response and set of psychosocial interventions. The possibility of comorbid presentation also requires consideration because this may have an impact on the risk of self-damaging behaviors.

When Depression Symptoms Remit, Quality of Life Improves — for Some

Joel Yager, MD reviewing *IsHak WW et al. Acta Psychiatr Scand 2014 Jun 23.*

Still, more than 30% of patients in pharmacologically induced remission reported below-normal quality of life, and 9% reported severe impairment.

Depression treatment studies usually focus on achieving symptom remission (minimal or no symptoms) or response (symptom reduction of ≥50%); few also consider overall quality of life (QOL). Using data from 2280 patients entered into STAR*D, a large, multistep treatment study of major depression (NEJM JW Psychiatry Apr 5 2006), investigators examined how treatment affected patient-rated satisfaction or enjoyment of mood, relationships, living situations, and physical health). Less than 2% of participants had baseline QOL scores within the normal range.

Among 812 patients whose depression remitted in level 1 (citalopram monotherapy), 79% had severely impaired self-rated QOL at entry. At remission, QOL scores were normal in 68% and severely impaired in 9%. Among 193 remitters in a 1-year follow-up, QOL impairment was severe in 14% at start of follow-up and in 13% afterwards.

Level-1 nonremitters generally had lower QOL self-ratings when entering later treatment steps. Among level-1 nonremitters, 89% had severely impaired baseline QOL, which remained severely impaired in 73% at the end of level 1. Among 221 nonremitters in follow-up, QOL was severely impaired in 41% at the start but 68% at 12 months.

Smaller Hippocampi in Depression Due to Childhood Maltreatment

Peter Roy-Byrne, MD reviewing *Opel N et al. Neuropsychopharmacology 2014 Jun 13.*

In both depressed and healthy people, hippocampal size is related to childhood maltreatment.

Depression has been associated with smaller hippocampi, possibly mediated by stress-induced increases in cortisol, although some studies have suggested that a small hippocampus may be a trait that predisposes to depression. These researchers used two methods to measure hippocampal size in 85 inpatients with rigorously diagnosed major depression (mean age, 37) and 85 age-matched controls without psychiatric histories.

All participants were assessed for childhood adversity with the Childhood Trauma Questionnaire (CTQ). Although depressed subjects had smaller hippocampi than controls, mean hippocampal size in both depressed and control groups was inversely correlated with estimates of childhood maltreatment according to CTQ scores. After adjustment for CTQ score, depressed and control groups showed no difference in hippocampal size.

Quetiapine for Borderline Personality Disorder?

Joel Yager, MD reviewing *Black DW et al. Am J Psychiatry 2014 Jun 27.*

Although improvement with low-dose quetiapine occurred, this 8-week study was too short to prove meaningful long-term value for the medication.

Study results on antipsychotic use in patients with borderline personality disorder have been conflicting, in part due to the many associated mood, anxiety, behavioral, and cognitive symptoms. In an industry-funded, multisite, double-blind study, academic researchers randomized 95 patients with borderline personality disorder to 8 weeks of extended-release quetiapine at 150 mg/day, 300 mg/day, or placebo (mean age, 29; 29% male).

Quetiapine dosing was started at 50 mg/day and gradually increased over several weeks. Exclusions were current substance dependence or recent abuse, recent suicidality, lifetime psychosis or neurological disorders, pregnancy, lactation, or previous nonresponse to atypical antipsychotics. Overall, 80% of patients had lifetime axis I disorder (mostly mood), and 32% had lifetime substance use disorders. Similar percentages in the groups dropped out; 67% were completers.

Response (≥50% reduction from baseline scores on a standardized scale) was achieved for total and some symptom scores in at least one post-baseline visit by 82% of patients on low-dose quetiapine, 67% on moderate-dose quetiapine, and 62% receiving placebo. At the last treatment visit, 82%, 74%, and 48%, respectively, were rated as responders; the number needed to treat for one patient to benefit was about three for low-dose and four for moderate-dose quetiapine. Sedation, changes in appetite (presumably increases), dry mouth, dizziness, and average modest weight gain were more likely at the higher dosage.

Psychiatric Disorders Are Common in Patients with Dizziness

Jonathan Silver, MD reviewing *Lahmann C et al. J Neurol Neurosurg Psychiatry 2014 Jun 24.*

Especially when there is no organic etiology

Complaints of dizziness, including vertigo, are common. Almost half are not explained by vestibular or neurologic disorders but are believed to be related to a psychiatric condition. Anxiety and depression also are very common in patients with vestibular migraines (VM), unlike patients with benign paroxysmal positional vertigo (BPPV). These researchers examined records of 547 patients with vertigo/dizziness (mean age, 55; 44% men), who received comprehensive neurological (including neuro-otological and neuro-ophthalmological) and standardized DSM-based psychiatric evaluations at a specialized treatment center.

Organic causes were found in 81% of patients; the most frequent causes were vestibular migraine (n=95), BPPV (n=87), and Meniere disease (n=81). About half of the study population received psychiatric diagnoses. The most common psychiatric disorders were anxiety/phobia (n=158), somatoform disorder (n=136), and affective disorder (n=104). Psychiatric disorders were more common when vertigo/dizziness lacked an organic etiology. Having a psychiatric disorder was associated with greater psychosocial impairment. Half of patients with vestibular paroxysmia and vestibular migraine also had psychiatric disorders.

Assessing and Enhancing the Effectiveness of Antidepressants

Steve Balt, MD, MS [2]
Column [3] | June 13, 2014 | Psychopharmacology [4], Depression [5], Major Depressive Disorder [6]
By Steve Balt, MD, MS [2]

With over 2 dozen FDA-approved antidepressants on the market, it is reasonable to ask: which antidepressants are most effective?

With over 2 dozen FDA-approved antidepressants on the market, it is reasonable to ask: which antidepressants are most effective? After decades of clinical experience and literally millions of prescriptions written over the years, it stands to reason that 1 or 2 agents have risen from the pack to outshine the rest.

Unfortunately, clinical experience shows this not to be the case. The general consensus is that despite their different mechanisms of action, all current antidepressants seem to have more or less the same effect. The functional equivalency of antidepressants is highlighted in practice guidelines and, understandably, serves as justification for restricted formulary access to more expensive agents.[1] As a result, most psychiatrists choose antidepressants not on the basis of efficacy, but rather on the basis of insurance coverage, adverse-effect profiles, or particular clinical features of depression (eg, melancholic, atypical, anxious features), for which some differences in efficacy do exist.

Efficacy vs effectiveness

The question of how well antidepressants work for the routine treatment of depression can be answered in terms of efficacy or effectiveness. An

efficacy trial asks the question, Does the drug work under ideal circumstances? Although such trials are usually brief (6 to 8 weeks) and interventions are standardized and rarely flexible, they serve as the basis for the FDA's approval of drugs.

"Effectiveness" concerns the success or failure of drugs in the real world. A true effectiveness study asks the question, Does the drug work under usual conditions? Effectiveness trials enroll a more heterogeneous population, often with comorbid mental illness, substance abuse, or other psychiatric diagnoses, and health care professionals are often free to offer concurrent therapies. As a result, effectiveness trials tend to have more generalizability, or external validity, to real patient populations.

Effectiveness trials help clinicians and policymakers select which medications work best for a given indication in real-world conditions. Surprisingly, despite decades of experience with antidepressants, information on their relative effective-ness is lacking, while health care costs continue to escalate. As a result, more emphasis is being placed on comparative effectiveness research, in which alternative treatments are compared under real-world conditions, and costs and adverse effects are measured in addition to clinical outcomes.

Effectiveness studies

Effectiveness trials are often large, expensive, and time-consuming. They sometimes take the form of a practical clinical trial in which multiple clinically relevant treatment regimens are compared across a large population of subjects. One such landmark study is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. In this NIMH-funded study, more than 4000 depressed patients in outpatient psychiatry and primary care practices received citalopram for up to 12 weeks; those who did not improve advanced to later phases that offered augmentation with, or a switch to, a second antidepressant or psychotherapy.[2]

Remission rates in step 1 were low (28%) and decreased further with additional steps. Cumulatively, two-thirds of patients entered remission after 4 steps.[3] Direct comparison of the effectiveness of antidepressants was not possible because of the overall lack of randomization and poor statistical power.[4] Despite the scope and initial aims of the study, no single antidepressant strategy or combination appeared more advantageous than any other.

Other effectiveness trials have yielded similar results. A 24-week trial that randomized patients to sertraline or citalopram found no significant difference between groups.[5] Another 24-week trial of 234 patients randomized to receive sertraline or fluoxetine also found no significant difference.[6] In a 2001 study, 573 patients were randomized to 1 of 3 SSRIs for 9 months; sertraline, paroxetine, and fluoxetine were equally effective.[7] Patients admitted to a German psychiatric hospital for treatment of depression were followed up for 10 weeks, and response and remission rates were 68.9% and 51.9%, respectively, again with no difference among individual antidepressant agents.[8] Effectiveness trials, therefore, seem to confirm the conventional wisdom that no single antidepressant works better than—or worse than—any other.

Meta-analyses of efficacy studies

Efficacy trials rarely resemble real-world conditions and, as such, tend to overestimate how well drugs work. Nevertheless, the aggregation of data from multiple efficacy trials can provide a suggestion as to the relative effectiveness of antidepressants.

In 2005, the Agency for Healthcare Research and Quality commissioned an exhaustive review of antidepressants and their use in MDD.[9,10] Close to 300 studies were reviewed, many of them randomized efficacy trials that compared one antidepressant with another. There was sufficient evidence to make 4 drug-drug comparisons: 3 found no significant difference between the two drugs, while another found a small reduction (1.25 points) in the Montgomery-Åsberg Depression Rating Scale (MADRS) score in patients taking escitalopram, relative to citalopram. Findings indicate that there were no significant differences in effectiveness of antidepressants, although individual drugs did differ in terms of onset of action and ease of dosing. A 2011 update found a similarly slight benefit of both sertraline and venlafaxine over fluoxetine, as well as confirmation of escitalopram's slight superiority over citalopram.[11]

In a review of 117 randomized trials involving 25,928 patients, Cipriani and colleagues[12] identified slight differences between certain pairs of antidepressants. Known as "network analysis," this technique permits comparisons of 2 drugs according to how well they perform against a common comparator. Specifically, the authors found that mirtazapine, escitalopram, venlafaxine, and sertraline had slightly greater odds of inducing a response than other antidepressants studied. They also compared relative acceptability of

antidepressants (by assessing dropouts) and found the most benefit for escitalopram and sertraline, but differences were slight and of questionable clinical significance.

Because a meta-analysis is only as good as the data on which it is based, these meta-analyses must be considered in light of the very real problem of selective publication. This is the tendency for favorable results to be published, while negative or neutral results are not. In an analysis of 74 antidepressant trials registered with the FDA between 1987 and 2004, Turner and colleagues[13] found that nearly half (36, or 48.6%) were negative, and the vast majority of these were either not published or were published in a way that made the drug seem favorable. Likewise, industry-sponsored studies are more likely to favor the manufacturer's drug, often because of nuances in experimental design.[14] While most researchers make every effort to include unpublished results in their meta-analyses, the "file-drawer" phenomenon of unpublished negative results may bias the conclusions of analyses that exclude the inaccessible data.[15]

Enhancing effectiveness

Data appear to confirm 2 stark truths about antidepressants. First, there seem to be no significant differences among them; although future research may uncover patient-specific biomarkers that favor one medication over another, none has yet done so. Second, and somewhat surprisingly, antidepressant effectiveness is quite low. Thus, in the absence of data that can predict the best antidepressant regimen for a patient, enhancing the effectiveness of an antidepressant seems to be the best strategy.

One strategy has nothing to do with antidepressants, but rather involves a reconsideration of what is being treated. Treatment-resistant depression may be better defined as "depression that is resistant to currently available treatments." Many of these refractory cases may lie on the bipolar spectrum. Study results show that bipolar depression responds poorly to antidepressants, although what counts as "bipolarity" has been the subject of some controversy.[16,17]

Depression may be multiple conditions, each deserving its own unique treatment approach. Findings suggest that much of the antidepressant response in mild to moderate depression may be due to placebo effect.[18] Similarly, patients with a history of trauma may do better with psychotherapy than with medications, while patients with significant

anxiety may not respond as well to antidepressants and their depression might resemble a "neurotic" subtype.[19,20]

Another way to enhance antidepressant effectiveness is to combine antidepressants or use augmentation agents. While combination strategies have intuitive appeal and offer great flexibility, they are not always supported by the available literature. In the Combining Medications to Enhance Depression Outcomes(CO-MED) trial, 665 patients with depression were randomized to receive bupropion plus escitalopram, venlafaxine XR plus mirtazapine, or escitalopram alone. Outcomes at 12 weeks, and again at 7 months, were the same across groups.[21] Similarly, while evidence exists for the efficacy of a wide range of augmentation strategies, other analyses have found relatively low effectiveness or excessive cost or adverse-effect burden of some of these approaches.[22,23]

The more important question may be more about whom we are treating rather than what we treat with. Recent interest in "personalized medicine" seeks to improve depression treatment by using new tools to more accurately identify whom we are treating. It has been estimated that 42% of the variance in antidepressant response can be explained by genetic variation.[24] This suggests that nearly half of a patient's response to an antidepressant may be due to his or her genetic profile. In reality, however, the genetic contribution likely involves an impractically large number of variants, each having a very small effect, that together contribute to the very complex phenotype of antidepressant response. Indeed, 2 meta-analyses, using genome-wide analysis to identify polymorphisms to predict treatment response, found only a 1.2% contribution or no contribution at all.[25,26]

Another pharmacogenomic approach is to characterize functional variations in patients' cytochrome P-450 enzymes. Classification of patients as "poor" or "rapid" metabolizers, for instance, may help predict medication choice or dosage. Unfortunately, these approaches are limited. With few possible exceptions, no evidence exists that blood concentrations influence antidepressant outcomes, and there are multiple nongenetic factors that influence drug metabolism, such as diet, other medications, and adherence. Existing studies that show benefit of pharmacogenetic testing are limited because clinicians are unblinded or randomization procedures are poor, a troubling fact given the high rate of placebo response to antidepressant treatment.

Not surprisingly, we can take advantage of patient preferences to enhance treatment outcomes. When patients in a clinical trial receive a treatment they prefer, response rates are significantly higher than when they are randomized to a non-preferred intervention.[27] Even when patients' preferences do not have any bearing on outcome, matching treatments with patients' preferences increases their willingness to initiate and adhere to a treatment plan.[28]

Clinical trials are often criticized because the ongoing, regular con-tact between patients and clinicians (frequent office visits, abundant personalized attention, etc) may inflate placebo response rates. Indeed, regular contact with health care pro-fessionals has a therapeutic effect in itself, as do patient expectations. When patients in a clinical trial know they will get 1 of 2 active drugs, response rates are one-third higher than when they know they may be randomized to placebo.[29]

Finally, the quality of the therapeutic alliance between prescriber and patient is sometimes a better predictor of patient outcome than which drugs are prescribed. One study found that "effective" prescribers obtained better outcomes with placebos than "less effective" prescribers with active antidepressants.[30] Asking "which" medication may be less important than the "meaning" of medication to both clinician and patient. The characteristics of communication between prescriber and patient, whether the patient perceives an internal or external locus of control over the outcome, and a host of other factors may be more important than which drug is prescribed.

Conclusion

The generally accepted view that all antidepressants are essentially equivalent in their effectiveness appears valid. Selection of the right antidepressant, therefore, may rely less on matching a patient to a specific medication, and more on a consideration of adverse-effect profiles or medication availability, or on a redefinition of the phenotype of depression altogether. The recent emphasis on personalized antidepressant prescribing seems warranted, but rather than taking a combination or pharmacogenomic approach to medication selection, clinicians should focus more on a personalized approach, establish realistic (but hopeful) expectations, and use patient preferences and beliefs to optimize outcomes.

Must Serum Testosterone Be Measured First Thing in the Morning?

Allan S. Brett, MD reviewing *Welliver RC Jr et al. J Urol 2014 Jul.*

Diurnal variation in serum testosterone appears to diminish after age 45.

Because a man's serum testosterone level varies diurnally, guidelines generally advise measuring it in early morning, when it tends to be highest. However, diurnal variation becomes less prominent as men age. In this study, U.S. researchers examined initial serum testosterone levels measured in 2600 men who attended an erectile dysfunction clinic. Results were analyzed according to patient age and according to the time blood was drawn (between 7 am and 2 pm; too few samples were drawn after 2 pm for accurate analysis).

In men younger than 45, diurnal variation was confirmed; mean levels were ≈600 ng/dL at 7 am, 500 ng/dL at 10 am, and 400 to 450 ng/dL by 2 pm. However, within each 5-year age grouping for older men (age, ≥45), mean serum testosterone levels differed only minimally at all times from 7 am to 2 pm.

Is Bipolar Disorder Linked to Leadership Qualities?

Joel Yager, MD reviewing *Kyaga S et al. Acta Psychiatr Scand 2014 Jun 25.*

This Swedish whole-population study suggests that individuals with bipolar disorders show the highest and lowest rates of leadership potential.

Many anecdotes and a few studies have suggested that individuals in leadership positions are at higher risk for bipolar disorder. In a Swedish epidemiological study, investigators examined this hypothesis by analyzing 1973–2009 census registry data for diagnoses and professions of patients and their healthy siblings and, in men only, compulsory military conscript recruitment records on IQ and semistructured personal interviews for "officer suitability," which were conducted among men with average or higher IQ (N=1,126,519).

The researchers limited their examination to executive professions and a "political profession" subgroup. There were 22,980 individuals classified as having "pure" bipolar disorder — i.e., no psychiatric comorbidities (42% male; mean age at onset, 42) — and 68,915 individuals classified as having "general" bipolar disorder — i.e., the disorder with or without comorbidities (39% male; mean age at onset, 41). Each patient and each sibling were matched with 10 healthy controls.

Compared with controls, men with pure bipolar disorder were overrepresented at both the highest and lowest ranks of officer suitability (odds ratios, 1.46 and 1.56), whereas their healthy siblings were overrepresented at only the highest rank (OR, 1.37). Patients with pure bipolar disorder were underrepresented in executive professions, but healthy siblings were overrepresented, particularly in political professions (OR, 1.85). Adjusting for IQ attenuated overrepresentation at the highest rank, suggesting that IQ partially mediated these associations. Patients with "general" bipolar disorder were overrepresented only in the lower strata.

Stress Reveals Connections Between the Brain and the Blood

Steven Dubovsky, MD reviewing *Heidt T et al. Nat Med 2014 Jul.*

Chronic unpredictable stress has profound physiologic effects.

It is well known that chronic stress, especially if it is unpredictable, promotes inflammation. To learn more, researchers conducted a series of experiments in mice and 29 medical residents.

The residents self-reported higher stress levels and had higher peripheral neutrophil, monocyte, and lymphocyte counts during their intensive care rotation than at baseline.

Compared with nonstressed controls, mice stressed for 3 weeks had similar blood-count findings as humans; these increases were associated with increased proliferation of bone-marrow stem cells that were differentiating into white cells. Stem cell proliferation was linked to norepinephrine activity in sympathetic nerves innervating blood vessels in bone marrow, apparently via a β3-adrenergic (but not a β2) receptor. In atherosclerosis-prone mice, stress increased macrophage progenitors in bone marrow, and this increased protease levels, inflammation, and cytokines in atherosclerotic plaques. These changes led to rupture-prone plaques.

Do Not Overlook Strong Social Risk Factors for Suicide

Peter Roy-Byrne, MD reviewing *Tsai AC et al. Ann Intern Med 2014 Jul 15.*

Social support and sense of belonging can be powerfully protective against suicide in men.

Suicide, a major public health problem with devastating effects on family and friends, is more common in men than women. Predicting risk has been difficult, with psychiatric diagnosis and psychological factors of limited utility. In a prospective epidemiological study, researchers have now examined the utility of social risk factors in predicting suicide in 34,901 men (mean age, 57; from narrow professional socioeconomic strata) followed from 1988 to 2012, during which 147 men died by suicide.

A social integration index was computed from seven questions on marital status, size of social network, frequency of social contact, religious participation, and participation in other social groups. Analyses controlled for competing mortality risks from medical illness and used antidepressant medication as a proxy for mental illness. Compared with respondents in the lowest quartile, those in the two quartiles with best social support/integration had significantly (≈40%–50%) lower risk for suicide; marital status, social network size, and religious participation were the strongest factors.

The Current Status of Transcranial Direct Current Stimulation as a Treatment for Depression

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May 07, 2014 | Neuropsychiatry [5], Depression [6], Major Depressive Disorder [7], Transcranial Magnetic Stimulation [8]

By William K. Silverstein, BMSc [2], Zafiris J. Daskalakis, MD, PhD [3], and Daniel M. Blumberger, MD, MSc [4]

Evidence has accumulated on the efficacy of transcranial direct current stimulation in major depression. The authors review its potential mechanism of action, findings from recent clinical trials, and potential role in the treatment of depressive disorders.

Major depressive disorder is a leading cause of disability worldwide, affecting an estimated 120 million people; the lifelong prevalence is 10% to 15%.[1,2] Depression leads to severe morbidity and is the leading cause of suicide. An emerging problem in the treatment of depression is the development of treatment resistance. Treatment-resistant depression (TRD) occurs in 15% to 35% of depressed patients.[3] In addition, TRD is associated with serious economic burden: the cost of treating TRD is 6 times higher than that of treating nonresistant depression.[4]

In response to the emergence of TRD, novel therapies have been developed as alternatives to pharmacotherapy and psychotherapy. These include brain stimulation therapies. Currently, ECT is the most effective: 50% to 70% of patients respond to

treatment. ECT is a first-line therapy for severe or psychotic depression. Despite its efficacy, however, many patients avoid ECT because of the negative public perception associated with it and the potential cognitive adverse effects.

In recent years, evidence has accumulated on the efficacy of transcranial direct current stimulation (tDCS). This article describes the history of its use for treating major depression and its potential antidepressant mechanism of action. In addition, we review findings from recent clinical trials and discuss the potential role of tDCS in the treatment of depressive disorders.

Antecedents and mechanisms

tDCS is a minimally invasive form of brain stimulation that does not induce seizures. During tDCS, a weak, direct electrical current (1 to 2 mA) is applied using 2 scalp surface electrodes that are covered by sponges and soaked in saline. Findings from preclinical studies suggest that tDCS may cause polarity-dependent alterations in cortical excitability and activity. Anodal stimulation increases cortical excitability and cathodal stimulation decreases cortical excitability.[5] The changes in cortical excitability are probably through respective depolarization and hyper- polarization of neurons. It appears that this effect can be attributed to a subthreshold modulation of resting membrane potential, and it can persist even after stimulation stops.[5,6]

As a result of its ability to alter cortical activity, scientists began investigating the utility of tDCS as a treatment for depression in the 1960s. The results from these studies were mixed, and methodological variability between studies confounded the findings; as a result, interest in tDCS waned after the 1960s. However, beginning in the 1990s, research into the use of brain stimulation therapies for depression grew exponentially. Renewed interest in tDCS as a treatment for depression has led to multiple studies that examined optimal treatment protocols and efficacy of tDCS.

MDD is a complicated disorder: its pathophysiology and etiology are not completely understood. However, one hypothesis asserts that in depression, there is a pathological abnormality and imbalance in the activity of the left and right prefrontal cortices: the left dorsolateral prefrontal cortex is hypoactive and the right dorsolateral prefrontal cortex is overactive.[7-9] tDCS may produce electrode-dependent changes in regional brain activity by ameliorating the pathological imbalance between the two hemispheres of the dorsolateral prefrontal cortex by enhancing the excitability of the left and reducing the activity of the right.

By applying anodal tDCS to the left hemisphere to augment activity and cathodal tDCS to the right hemisphere to reduce activity, the pathological imbalance of activity in the brain may be restored to resolve the depression. While the protocol of stimulating both the left and right dorsolateral prefrontal cortices has been used in some studies, in others, anodal tDCS was applied to the left dorsolateral prefrontal cortex and cathodal tDCS was applied to a neutral region, such as the right supraorbital region, the contralateral orbit, or the contralateral cortical area.[10-13] One of the hypothesized rationales for use of these protocols is to restore the physiological intrahemispheric and interhemispheric balance.

Recent clinical trials

Several open-label studies and randomized controlled trials have been conducted to examine the efficacy of tDCS in treating depression. Most of these studies demonstrate that active tDCS is effective in reducing depressive symptoms.[11,14,15] The efficacy of tDCS alone was shown to be similar to that of a relatively low average dosage (50 mg/d) of sertraline.[16] In this factorial study, the combination of sertraline and tDCS led to an additive response that was superior to sham tDCS and placebo, to tDCS alone, and to sertraline alone. This suggests that combining tDCS with other antidepressant treatments

may be a method of enhancing outcomes and that the efficacy of tDCS may be comparable to that of first-line antidepressants, which may reduce the burden of TRD.

Findings also indicate that tDCS is effective in patients with mild to moderate depression that is not treatment-resistant.[11,17] The adverse effects associated with tDCS appear to be mostly limited to headaches and itchiness and redness at the site of stimulation, which are significantly less severe than the cognitive effects associated with other brain stimulation treatments, such as ECT.[18-20] In addition to its potential clinical utility and minimal adverse-effect profile, tDCS appears to improve cognitive performance.[21,22]

There is much discussion as to what the optimal time and stimulation frequency for tDCS treatment should be. Earlier studies used lower-amplitude stimulation (1 mA), but larger amplitudes (2 mA) are now being used. Higher stimulation amplitudes elicit a larger cognitive effect than do lower amplitudes.[23] The effects of tDCS were also shown to be cumulative, which led to an increase in the number of treatments in various protocols.[24]

Earlier studies used once-daily tDCS for 5 alternate days; more recent studies used tDCS twice daily for 5 consecutive days or once daily for 10 consecutive weekdays.[11,14,15] The next generation of studies administered treatments for up to 20 consecutive days.[25] Still more recent studies have extended the treatment course to 6 weeks or 30 treatments.[26] The extended duration of treatment led to enhanced efficacy, with remission of symptoms for at least 1 month. While replication is needed on the duration and number of treatments, it appears that enhanced treatment outcomes are associated with more intense stimulation and an increased number of treatment sessions.

Although the aforementioned trials have shown positive results, other findings suggest that multiple treatment failures, use of higher doses of benzodiazepines, and a failed course of ECT herald a worse response to tDCS.[10,12-14] No differences were seen in comparison studies of tDCS and sham stimulation.[10,27] The lack of multicenter,

randomized, controlled data limits the ability to advocate the treatment to the broad population of patients with depression. In addition, there are no studies that compare tDCS with other brain stimulation treatments (eg, repetitive transcranial magnetic stimulation and ECT).

The heterogeneity of patients in the various trials of tDCS makes it difficult to come to a definitive conclusion on the value of tDCS as a treatment for depression. Because the sample size was relatively small in many of the studies, the results of these trials need to be treated with caution. In addition to the small sample sizes used, few trials have looked at whether the antidepressant effects persist after the acute phase of treatment.[11,12,14,26] Thus, it is not known if the antidepressant effects exerted by tDCS are lasting or if maintenance treatments are necessary.

There is still a lack of consensus on the placement of electrodes that leads to optimal treatment outcomes, although there have been reductions in depressive symptoms with anodal stimulation of the left dorsolateral prefrontal cortex and cathodal stimulation of the right dorsolateral prefrontal cortex, or anodal stimulation of the left dorsolateral prefrontal cortex with a neutral region.

Although study results overall have been promising, additional research is needed before tDCS can be adopted in the broader clinical context. Research should focus on establishing the optimal stimulation parameters for tDCS. Adequately powered, randomized, controlled trials with longer follow-up times are needed to establish the long-term antidepressant effects of tDCS. Studies that examine biomarkers of treatment response to tDCS are necessary to gauge which patients will respond to treatment.

Conclusion

tDCS is an appealing treatment for depression because of its relative safety and efficacy profiles coupled with the fact that it is relatively inexpensive. This has spurred interest in the do-it-yourself (DIY) community, leading to the proliferation of DIY tDCS devices being sold on the Internet. Many of the Web sites offer either inexpensive tDCS devices or instructions on how to assemble a device using a 9V battery and $50 worth of basic electronic parts.

The proliferation of these DIY devices is worrisome because unsupervised tDCS use can impair cognitive function, interfere with concomitant treatments, and result in long-lasting unintended and undesirable effects.[28] Scientists, treatment providers, and regulators need to collaborate on drafting policy that ensures the safety of tDCS for users while simultaneously not discouraging use of DIY or relatively inexpensive devices.

tDCS appears to have tangible antidepressant effects. It is a promising therapy because of its minimally invasive nature and relatively benign adverse-effect profile. That said, its use appears to be limited to patients with mild to moderate depression; it is not for patients with higher degrees of treatment resistance. It could also be effectively used as an add-on therapy to pharmacotherapy and psychotherapy to optimize treatment outcomes.

Further research is needed to examine the utility of tDCS as a front-line treatment for more severe forms of depression. Currently, we would not recommend using tDCS as a first-line brain stimulation therapy for severe and treatment-resistant forms of depression. However, for now, it seems reasonable to consider tDCS as a treatment for patients with mild to moderate depression without treatment resistance, or to use it to enhance the first-line response rates when combined with pharmacotherapy or psychotherapy.

Psychotherapy for Conversion Symptoms?

Steven Dubovsky, MD reviewing *LaFrance WC Jr et al. JAMA Psychiatry 2014 Jul 2.*

Eclectic psychotherapy might work — if patients accept that their symptoms are psychogenic.

Psychogenic nonepileptic seizures (PNES, pseudoseizures) are conversion symptoms involving seizure-like movements in patients with normal electroencephalographic results. In this 4-month study on whether treatment affects PNES frequency, 38 patients with PNES and no epilepsy were randomized to one of four approaches: treatment as usual, sertraline (dose, ≤200 mg/day), 12 weekly sessions of manualized "cognitive-behavioral therapy–informed psychotherapy" (CBT-ip), or CBT-ip plus sertraline.

CBT-ip involved presenting the diagnosis; elements of education, behavioral analysis, cognitive therapy, interpersonal therapy, mindfulness, and dynamic psychotherapy; and teaching coping skills. Data from 34 patients were analyzed.

Both psychotherapy and psychotherapy/sertraline were associated with significantly fewer self-reported monthly seizures. The reduction in seizure frequency with sertraline was not statistically significant. Group numbers were too small for analyses of secondary measures, with most not corrected for multiple comparisons.

Discontinuation of Smokeless Tobacco and Mortality Risk after Myocardial Infarction

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3. Lars Lind1;
4. Karl Michaëlsson1;
5. Bertil Lindahl1;
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Abstract

Background—Based on indications of increased risk for fatal myocardial infarction (MI) in snus users, we hypothesized that discontinuation of snus use after an MI reduces mortality risk.

Methods and Results—All patients who were admitted to coronary care units for an MI in Sweden between 2005 and 2009 and were under the age of 75 underwent a structured examination two months post-discharge (the baseline of the present study). We investigated risk of mortality in post-MI snus quitters (n=675) relative to post-MI continuous snus users (n=1799) using Cox proportional hazards analyses. During follow-up (mean 2.1 years), 83 participants died. The mortality rate in post-MI snus quitters was 9.7 (95% confidence interval 5.7 to 16.3)/1000 person-years-at-risk and in post-MI continuous snus users 18.7 (14.8 to 23.6)/1000 person-years-at-risk. Adjusting for age and gender, post-MI snus quitters had half the mortality risk of post-MI continuous snus users (hazard ratio 0.51; 95% CI 0.29 to 0.91). In a multivariable-adjusted model, the hazard ratio was 0.57 (95% CI 0.32 to 1.02). The corresponding estimate for post-MI smoke quitters vs. post-MI continuous smokers was 0.54 (95% CI 0.42 to 0.69).

Conclusions—In this study, discontinuation of snus use post-MI was associated with a nearly halved mortality risk, similar to the benefit associated with smoking cessation. These observations suggest that the use of snus post-MI should be discouraged.

Telepsychiatry Is a Team Sport

Daniel W. Knoedler, MD [2]

Column [3] | June 24, 2014 | Telepsychiatry [4], Career [5]

By Daniel W. Knoedler, MD [2]

To run an effective telepsychiatry practice, a solid partnership between skilled personal on-site with patients and the psychiatrist on the other end of the call is a must.

Telepsychiatry is a team sport. To run an effective practice, you need skilled people on-site with the patients. The on-site staff needs to be able to do more than just get the patient into the correct room and call the psychiatrist. The on-site staff needs to be able to assess the things that you, as the telepsychiatrist, would not be able to assess: Does the patient smell of alcohol? Did he or she interact with the staff at the front desk, or with the other patients in the waiting room, in such a way that you should be made aware? Is there a family member in the waiting room who should be included in the appointment? Does the patient have a medication list that needs to be deciphered? Does the patient's behavior suggest that there might be a safety concern, either for himself or for the staff? Are there physical signs that you might notice in person

that might not be evident on video, such as rash or exophthalmos? The level of training and expertise of the on-site staff needs to be clearly understood by the treating physician.

We need to be aware, also, of the increased stress that the staff who are actually with the patients feel: in telepsychiatry, the psychiatrist is not on-site to help if some difficult event occurs. It may be the psychiatric nurses and aides who tackle the patient when a crisis occurs, but the team still sees the psychiatrist as the one who ultimately needs to make critical treatment decisions.

Telepsychiatry is good for psychiatrists. It offers the possibility of working from home, and of working somewhere warm in the winter and somewhere that's not too hot in the summer. It gives psychiatrists an opportunity to rejuvenate their careers in an interesting fashion, and to become proficient with a new set of skills using new technology. It may be that telepsychiatry will increase the shrinking pool of available psychiatrists, since some psychiatrists may choose to practice longer if telepsychiatry allows them to accommodate their own physical limitations as they age. Telepsychiatry may also allow younger psychiatrists to work more hours if the option of working from home creates greater flexibility for child care or a more satisfying ability to interact with family during the day.

Is telepsychiatry good for patients?

All else being equal, I believe that having a psychiatrist on-site, in person, in the room, is better for most patients than having a telepsychiatry session with a psychiatrist. (Of course, for some patients it will not make a difference; other patients may feel that telepsychiatry is less threatening than a live interview.) Telepsychiatry is enjoying a boom, but that is primarily, in my opinion, because there is a shortage of psychiatrists. If there were a surplus, I believe the demand for telepsychiatry would be much smaller.

A relevant question is whether telepsychiatry for a rural clinic is better than the grand tradition of the traveling, itinerant psychiatrist who spends a day or two at a time, in person, in small clinics, traveling from small town to small town on a regular schedule. The answer, at least for most patients, is that telepsychiatry is better for the psychiatrist, but not necessarily better for the patient. One exception might be in very sparsely populated rural areas, where a patient might have to travel long distances even to get to a rural clinic. In that situation, a telepsychiatrist might be able to see a patient in a very small town—a town too small to support even an occasional full day of psychiatric time—perhaps by videoconferencing into the patient's home.

Consider the costs

Telepsychiatry is costly. In addition to the videoconferencing equipment, a telepsychiatrist needs two offices: one for the psychiatrist, and one for the patient. A telepsychiatrist also needs someone to be on-site and available to the patient at all times. If you have one technician or nurse at the patient end of the interaction, and that person calls in sick, goes on vacation, or even just goes to lunch, your practice will grind to a halt. You need a backup staff on the patient end.

You also need ongoing IT support—a little if you are lucky, but a lot if you are not! To minimize the risk of canceling patients because of a technology issue, your IT support needs to be readily available. Having a nurse with extensive mental health experience available at the patient end of the interaction is highly desirable and addresses many of the concerns raised by having the psychiatrist off-site.

Prescriptions can be handled by using an electronic prescribing service, such as Allscripts. Controlled substances that require a written prescription involve more effort, including a combination of calling prescriptions into a pharmacy and mailing written prescriptions.

Implications for the doctor-patient relationship

Should telepsychiatrists videoconference into a patient's home, allowing the patient to be seen without even leaving his home? Can we use telepsychiatry to re-create the home visit that was such a tradition of doctors in the past? Perhaps there are patients who would benefit, but it seems as if telepsychiatry into a patient's home might be a very different kind of interaction than what we are used to. Going to the doctor's office, negotiating the reception desk and the waiting room, and sitting in a professional office must surely have significant meaning in the therapeutic relationship. Seeing a patient in his home via videoconferencing also involves the complicated issues of the home environment: privacy, technical equipment, the patient's feelings about the psychiatrist being "present" in his home, and the expanded potential for disruptions.

I recently decided to retire from my full-time telepsychiatry position with the VA and return to my previous full-time job as the Health and Human Services psychiatrist for Sheboygan County, Wisconsin. I will be on-site for at least half the year at Sheboygan County, and doing telepsychiatry for Sheboygan County from someplace warm for the rest of the year.

There are, undoubtedly, psychiatrists who will thrive doing telepsychiatry from home full-time; my experience has taught me that I am not one of them. Full-time telepsychiatry is a diet that is a bit too rich for me; tiramisu is delicious, but not tiramisu for breakfast, lunch, and dinner! I am looking forward to working with my colleagues at Health Human Services again, live!

Israel has received over $121 bn US aid since 1949

LAHORE: Having killed over 1,500 unarmed Palestinians during the last 26 days, Israel has received over $121 billion in non-inflation-adjusted bilateral assistance from the United States of America between 1949 and April 2014, reveals a recent report prepared by the American Congressional Research Service.

According to the April 11, 2014 report prepared for Members and Committees of the US Congress by Jeremy Sharp, a specialist in Middle Eastern Affairs, this figure of $121 billion thus makes Israel the largest cumulative global recipient of US foreign assistance since World War II.

In his report, Jeremy Sharp had stated: “Almost all US bilateral aid to Israel is in the form of military assistance, although in the past Israel had also received significant economic assistance. Strong congressional support for Israel has resulted in Israel receiving benefits not available to any other countries; for example, Israel can use some US military assistance both for research and development in the United States and for military purchases from Israeli manufacturers.”

He had further asserted: “In addition, US assistance earmarked for Israel is generally delivered in the first 30 days of the fiscal year, while most other recipients normally receive aid in installments, and Israel (as is also the case with Egypt) is permitted to use cash flow financing for its US arms purchase.”

According to Israel’s oldest newspaper “The Haaretz,” this nominal aid figure of $121 billion is actually equivalent to over $233.7 billion, if it is adjusting for inflation.Founded in 1918 and published both in Hebrew and English languages, “The Haaretz” had also quoted a 2013 statement aired by Moshe Arens, a former Israeli Foreign Minister,

Defense Minister and the country's ambassador to Washington DC, which had clearly spelt out the fact that Israel happened to be the largest single recipient of American foreign aid.

Interestingly, just a fortnight ago on July 15, 2014, the United States Senate had shown its strong "love and affection" for Israel by approving an increase in its financial aid to the recipient nation's Iron Dome anti-missile system.

The US Senate Appropriations Defence subcommittee had agreed to allocate $351 million to finance the Israeli anti-missile system during fiscal year 2015 beginning on October 1, compared to $235 million in 2014.

Interestingly, the incumbent US President Barack Obama had requested only $179 million to support the system in 2015.A research conducted by "The News International" by taking into account some similar articles and news stories appearing in various prestigious American media outlets also reveal that US aid relationship with Israel is unlike with any other in the world.

The first US aid to Israel had arrived in 1949 and was used for such basic purposes as buying food and absorbing Jewish refugees. It began to expand a decade later with the first military aid. It grew gradually from a base of $100 million (in nominal terms) in 1949, before taking off after the Yom Kippur War and the signing of the Camp David agreements.

Since then, US aid has been about $3 billion annually, of which $1.8 billion is military assistance with the rest for civilian purposes. In 1998 Benjamin Netanyahu, in his first term as Israeli Prime Minister, had led a drive to convert the civilian portion to military aid, totaling $2.5 billion to $3 billion a year.

Israel had gone on to receive the most aid in the 1970s between the 1973 Yom Kippur War and the 1979 peace agreement with Egypt. For signing the accord with Egypt, Israel received its largest-ever amount of aid some $15.7 billion in grants and loans after adjusting for inflation (it was $4.7 billion at the time), which was used to fund the transfer of army bases in the Sinai Peninsula back into Israel.

The extent of American “generosity” towards Israel can also be gauged from the fact that the year 1974 had seen particularly high level of American assistance flowing to Israel.This was the year when the United States had helped Israel reestablish its military standing after the losses it suffered in the Yom Kippur War.

In inflation-adjusted terms, Israel received $12.4 billion ($2.6 billion in nominal terms) during 1974. In 1976, Israel had received another $9.6 billion ($2.3 billion in nominal terms).

The above-mentioned numbers and statistics do not include loan guarantees amounting to about $19 billion that Washington has granted Israel in recent years to make it easier for it to borrow overseas. It also doesn’t include the transfer of surplus military equipment to Israel.

Research further shows that between 1974 and 1989, some $16.4 billion in the American military loans to Israel were converted to grants and that this was the understanding from the very beginning.

Indeed, a good amount of the past US loans to Israel were eventually forgiven by the Congress, which has undoubtedly helped Israel’s often-touted claim that they have never defaulted on any American government loan!

Witch hunt against Israel's war critics

In Israel, dissent against the war in Gaza is bitterly quashed. The few who speak out complain of being harassed, intimidated or even sacked. The once mighty left has disappeared.

It has been Israel's deadliest conflict in years. More than 1,960 Palestinians were killed and 64 Israeli soldiers died fighting what some see as an unwinnable war.

And yet the only significant protest in Israel so far saw thousands late on Thursday demand an end to Hamas rocket attacks, dissatisfied with the status quo after ground troops pulled out and a ceasefire was extended.

Liberal newspaper Haaretz decried on Friday what it called a "witch hunt" against leftists and civil rights organisations after the director of the national service administration, Sar-Shalom Jerbi, told rights group B'Tselem it was being blacklisted as an employer.

"I feel obligated to exercise my power and stop the state assistance provided to an organisation that works against the state and against soldiers who are heroically giving their very lives to protect the safety and well-being of all citizens," Jerbi wrote in a letter.

He accused B'Tselem of disseminating lies and slander, endangering the state and publishing information that encourages Israel's enemies and leads to violent anti-Semitic acts against Jews around the world.

The rights group denounced the move as an attack on Israeli democracy, and asked supporters to sign an online petition to support freedom of expression and democracy.

Yizhar Beer of the Keshev Centre for the Protection of Democracy in Israel says it has never been more difficult to voice dissent in a country which prides itself on being the only democracy in the Middle East.

Israeli public opinion has overwhelmingly supported the war. A poll carried out by The Israel Democracy Institute last month said 95 percent of Israeli Jews believed the offensive was just. In a country with compulsory national conscription, almost everybody has a friend or relative in the army. Hamas rocket attacks have tormented millions of Israelis, inflicting fear and panic in border communities, regardless of the fact that hundreds are shot down and just three civilians have been killed since July.

In Israel, as in most countries during time of war, the local media have been patriotic champions of the offensive, uniting behind their boys on the frontline, sending them presents, highlighting the suffering of Israeli citizens and downplaying suffering on the other side.

The few who have spoken out of line have been threatened or denounced as traitors.

After Haaretz commentator Gideon Levy accused air force pilots of perpetrating “the cruelest and most despicable deeds” against Gaza’s “weakest and most helpless,” his employer hired him bodyguards.

Readers cancelled their subscriptions, people stopped in the street to insult him and government whip Yariv Levin denounced him as a liar, a “mouthpiece of the enemy” who should be put on trial for treason.

“I have never faced such aggressive reaction, never,” Levy told AFP in his cramped office at Haaretz in Tel Aviv, away from the coffee shops where he fears being insulted.

“Nobody cares here about the suffering of Gaza. More than this, if you dare to express empathy you are a traitor,” he said.

Pakistani doctors, relief supplies stopped at Gaza border

Karachi

A number of Pakistani specialists and the medical supplies intended for Palestinians have been stopped by Egyptian and Israeli authorities at the Gaza border.

“Many trauma surgeons, orthopaedics, paediatricians, psychologists and anaesthetics had volunteered to go to Gaza but the Egyptian and Israeli governments are not allowing them to go inside the besieged area,” Pakistan Islamic Medical Association (Pima) President Dr Sohail Akhtar told The News on Thursday.

The Gaza health ministry had appealed to the Federation of Islamic Medical Associations (Fima) to provide 20 ambulances, medical supplies, health equipment and specialists after over 9,000 people were injured besides the 1,900 killed in a month-long brutal Israeli assault in Gaza.

Pima arranged four ambulances as well as medical supplies worth millions of rupees to provide medical assistance to thousands of wounded Palestinians.

Pima currently leads Fima, an alliance of 35 international medical associations of the world. Pima’s Dr Tanveer Zubairi is the Fima chairman.

“Fima has [also] arranged 20 state-of-the-art ambulances, which are ready to be shifted to Gaza at Egypt’s Rafah border crossing, but Israel has let only four of them to go into Gaza,” he said. “Medical supplies for thousands of patients are also awaiting permission at the Cairo airport to be transported into Gaza.”

So far Israel has let three convoys of medical supplies, two from Fima and one from Doctors Worldwide, inside Gaza. Only 13 doctors, including eight Sudanese specialists and five Arabs, have been allowed to enter the Gaza strip to assist local doctors. Hundreds of doctors from all over the world, including United States and Pakistan, are awaiting permission to help the wounded Palestinians

“In the last few weeks, dozens of Pakistani specialists have contacted PIMA and expressed their willingness to go to Gaza,” Akhtar added.

“The Israeli government has told Fima it would allow ambulances into Gaza on their conditions,” the Pima president claimed. “First, the ambulances should be bought from Israel which they are selling on exorbitant rates. Second, the ambulances should be given to people nominated by Israel, to which Fima has refused.”

Five WHO health kits, each enough for medical needs of 50,000 people, are also stranded in Egypt, according to him.

Fima, he said, has decided to either construct a hospital in Gaza to treat the wounded or to reconstruct one of the health facilities destroyed in the shelling by Israeli forces.

Around 12 hospitals and 5 primary healthcare facilities were destroyed by Israel, killing patients and doctors inside them and worsening the healthcare system in the besieged territory.

Akhtar said Pakistani doctors as well as people were donating generously for the Palestinians and the fund-raising campaign would continue without any break.

He also appealed to government to use its influence on the Egyptian government to let medical supplies, medicines, equipment and health experts into Gaza from the Rafah border so that thousands of lives could be saved.

MQM Rabita Committee leaders removed,reinstated within hours

Karachi

A few hours after a notification was issued on Sunday for their removal, the Muttahida Qaumi Movement's Coordination Committee retracted its orders and announced the reinstatement of Engineer Nasir Jamal and Dr Sagheer Ahmed to their positions.

Both senior leaders had been relieved of their duties with the committee in view of their increasing personal and official responsibilities. However, the committee later issued a statement to reinstate Jamal as the deputy convener, while also requesting him to continue his work with the party's central information and news committees.

Dr Ahmed was also advised to continue serving as the provincial health minister and make all possible efforts to bring about improvements that would facilitate Sindh's people.

Doctors tackle damaged minds in Gaza

In a ward at Shifa, Gaza's largest hospital, child therapist Rabeea Hamouda is trying to elicit a response from two small brothers, Omar and Mohammed, aged three and 18 months, hoping for some words or perhaps a smile.

For seven straight minutes the children, peppered with burns and shrapnel wounds sustained in Israeli shelling that hit their home in north Gaza, stare at him blankly, emotionless.

Eventually, as Hamouda gently teases them, pretending to mix up their names and holding out a present while another counsellor sings quietly, a smile creeps across Mohammed's face and the older one, Omar, cries out his name.

"At the beginning, Omar was not responding to us at all, he was not even willing to say his name," explains Hamouda, who heads a team of 150 psychotherapists working for the Palestinian Centre for Democracy and Conflict Resolution in Gaza.

"Big progress has been made with these children," he says with a sense of relief and quiet accomplishment. "At the beginning they did not talk, they refused to communicate. But now, with the sixth session, we are witnessing good progress.

"Omar and Mohammed are just two of the 400,000 Gazan children the United Nations estimates are in need of psychological care as a result of not just the latest war in the territory but the three previous conflicts fought with Israel since 2006.The most recent conflagration has been the deadliest, with 1,945 Palestinians killed, many of them civilians and including an estimated 457 children. On the other side of the border, some 64 Israeli soldiers and three civilians have been killed.

Whether the result of Israeli air strikes, having parents or relatives killed before their eyes, hearing militants firing rockets from their own towns or themselves being wounded, the psychological trauma for Gaza's young is profound.

The symptoms range from nightmares, bed-wetting and behavioural regression to more debilitating mental anxiety, including an inability to process or verbalise experiences.

There is also deep trauma on the other side of the border, with tens of thousands of Israeli children mentally disturbed by the regular rocket fire from militants during the month-long war and over the seven years since Hamas seized control of Gaza.

While the conflict's destruction of buildings and livelihoods is clear to see and documented daily in television footage, the damage to minds is mostly invisible, yet can have far more damaging and longer-lasting consequences.

"The first time a child goes through a traumatic event like a war it's just deeply terrifying," said Chris Gunness, the spokesman of the United Nations Relief and Works Agency, which has 200 psychotherapists working in up to 90 clinics in Gaza.

"The second time is terrifying-plus-one because the child remembers the worst parts of the last war as well as the impact of the current one. Then the third time is plus-plus as the compounded memories of conflict build up.

"This time, for an eight- or nine-year-old child in Gaza, it's very, very intense indeed because there is this cumulative toll of trauma from repeated conflicts since 2006."

Hamouda and his team, like other psychotherapy units working across the small territory - home to an estimated 1.8 million people, more than half of whom are aged under 18 - can barely cope with the number of patients requiring help.

The treatment is by necessity basic - an effort to draw children out, to have them paint pictures of their experiences or emotions, to get them to verbalise their circumstances.

While a lot can be achieved with such simple techniques, many more require longer-term, personalised psychological care because of the enormity of the mental damage suffered.

“First we provide wounded and traumatised children with immediate pyscho-social support and we give parents some guidance on how to deal with them,” says Hamouda. Then there is home care and follow up for the more severe cases.

“Houses can be rebuilt and some physical wounds can be healed, but the people’s psychological condition needs more than money and time,” he says. “It needs a big effort and persuasion, and overall it needs calm and stability.”

One of Gaza’s most successful trauma assistance projects is the Gaza Community Mental Health Programme, launched in 1990.

Hassan Zyada, a psychologist with the project, describes the latest conflict as easily the worst since 2006, with scores of Palestinians having lost multiple family members.

“Our expectation is that more than 30 percent of the people here in Gaza will develop a psychiatric disorder,” he said.

Even health professionals are not immune. Six members of Zyada’s own family were killed during the war: his mother, three brothers, a sister-in-law and a nephew. He is now receiving counselling from the clinic’s chief therapist.

“It is a really traumatic loss and it is not easy for me to deal with,” he said, adding that several others on the team had suffered similar experiences.

Free Medical Camps

Karachi Psychiatric Hospital Organized a Free medical camp at Haji mureed goth.

Doctors are checking the patients

Event on 14th of August

Dr. Syed Mubin Akhtar MD-Karachi Psychiatric Hospital,
Muhammad Mujahid Barkati Patron Tehreek Nifaz Urdu,
Naseem Ahmed Shah Vice President of Tehreek Nifaz-e-Urdu,
Shabbir Ansari, editor Nifaz e urdu, Saeed baig, Publicity Advisor,
Syed Saeed Hasan, Secretary Nifaz-e-Urdu,
Laeeq Ahmed (ex MNA), C.E.O. Rashid Hasan, G.M. Shamshad Chand & others