

# Psychiatry

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## POSTGRADUATE EDUCATION NEWSLETTER

NOVEMBER 2003

### Upcoming Courses

Upcoming continuing education courses in the year 2004, offered by the Department of Psychiatry at the Massachusetts General Hospital, are as follows:

#### Child & Adolescent Psychopharmacology

Friday-Sunday, March 5-7, 2004  
Westin Hotel, Copley Place, Boston

#### Psychiatric Care of the Medically Ill: A Review of Psychosomatic Medicine

Friday-Sunday, June 4-6, 2004  
Westin Hotel, Copley Place, Boston

#### Psychiatry: A Comprehensive Update & Board Preparation

Monday-Saturday, September 27-October 2, 2004  
Westin Hotel, Copley Place, Boston

#### Psychopharmacology

Thursday-Saturday, October 21-23, 2004  
Westin Hotel, Copley Place, Boston

#### Aggressive, Resistant & Delinquent Youths

Friday-Sunday, November 12-14, 2004  
The Fairmont Copley Plaza, Boston

#### Home Study on Audio Cassettes

Aggressive, Resistant & Delinquent Youths: Meeting the Treatment Challenges  
Attention Deficit Hyperactivity Disorder Across the Life Span  
Natural Remedies for Psychiatric Disorders: Considering the Alternatives  
Psychiatric Neuroscience: A Primer for Clinicians  
Psychiatry: A Comprehensive Update & Board Preparation

### FOR MORE INFORMATION:

For more information about this and other courses presented by the Department of Psychiatry at MGH, please visit our web site, call, write, or email our administrative staff, at:

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## Psychopharmacology

October 16-18, 2003

### COURSE DIRECTORS:

Jerrold F. Rosenbaum, M.D., Maurizio Fava, M.D., and John B. Herman, M.D.

### COURSE ADMINISTRATIVE STAFF:

Stephanie Lipka Hackett, Gail Dickson, M.P.A., Arlene Lietz and Katherine Pike, M.S.W.

The Massachusetts General Hospital's Department of Psychiatry, headed by Dr. Jerrold F. Rosenbaum, presented this 27th annual course on Psychopharmacology. Constantly refined in response to the needs of over 11,000 course graduates, our seasoned faculty blended their expert knowledge with a clear lecturing style and a detailed syllabus. Twenty-four hours in category I credit towards the AMA Physicians Recognition Award, 24 continuing education credits for psychologists, and contact hours for the continuing education of nurses were available. The course, with its renowned faculty of clinician-researchers presented a course designed for clinicians who wished to re-tool and refine their knowledge of "state-of-the-art" practice in order to deliver the best care to patients they treat everyday.

Each of the approximately 760 attendees of this three-day curriculum (held at the Westin Hotel, Boston, MA) received a comprehensive syllabus, which contained lecture outlines, a printout of slides presented, and reprints of key references.



Here are some facts from the MGH's Psychopharmacology course:

## THE TREATMENT OF BIPOLAR DISORDERS (TWO-HOURS)

Gary Sachs, M.D.

Dr. Sachs provided a vibrant, graphically intense overview of mood disorders, covering their prevalence, clinical manifestations, and current treatments.

- \* Mood disorders are common, deadly, and treatable.
- \* The lifetime prevalence of bipolar I disorder is 1%; when the rates of bipolar I, bipolar II, and cyclothymia are combined, the prevalence reaches 3%.
- \* The chief complaint for most patients with a manic episode (mixed) is depression.
- \* Initial treatment of mania often targets hypervigilance, restlessness, agitation, and aggression.
- \* If the first presentation of a mood disorder is mania, there is a 95% chance of recurrence.
- \* Once an individual has had three or more episodes, the chance of subsequent recurrence is 99%.
- \* The risk of suicide in untreated individuals with bipolar disorder is 30 times that of those in the general population; 15% to 20% of untreated bipolar patients die by suicide.
- \* Peak times for suicide in those with bipolar disorder are in May and October.
- \* Only 27% of those diagnosed with bipolar disorder receive treatment.
- \* On average the euthymic interval after the first episode of bipolar disorder is 4.5 years; it is only 2.8 years after the second episode, and 1.5 years after the fifth episode.
- \* It takes only one episode of mania for a bipolar disorder to be diagnosed, no matter how many times a person has been depressed.
- \* One should not rely on a patient's denial of manic symptoms; it is important to get reliable information from other sources.
- \* A consensus practice guideline (with 61 experts surveyed) described the current state-of-the-art for treatment of bipolar disorders.
- \* Lithium is equivalent to valproic acid for treatment of mania.
- \* Standard mood stabilizers include lithium, valproic acid, carbamazepine, and possibly lamotrigine.
- \* Unlike carbamazepine, oxcarbazepine has few drug interactions and is not associated with auto-induction of its metabolism.
- \* Reasonable treatments for bipolar disorder, for which there is little data, include use of anticonvulsants (e.g., gabapentin, tigabine, and acetazolamide), adrenergic blockers (e.g., clonidine, propranolol, and guanfacine), calcium channel blockers (e.g., verapamil, nimodipine, and amlodipine), atypical antipsychotics (e.g., clozapine and quetiapine), hormonal agents (e.g., thyroxine, estrogen/progesterone, and tamoxifen) and others (e.g., tryptophan, choline, and donepezil).
- \* In bipolar disorder, antidepressants can induce mania.
- \* Mania with psychotic episodes has a worse prognosis than mania without psychosis.
- \* Triggers for mood switches in bipolar patients include sleep loss, alcohol and substance abuse, rapid discontinuation of lithium, antidepressant use, interpersonal conflicts, loss of a support system, east to west travel, and change of seasons.
- \* Rapid cycling involves four or more episodes in a one-year period or two or more complete cycles.
- \* The single most effective treatment for treatment of a rapid cycling mood disorder is discontinuation of antidepressants.
- \* Approximately 10% of individuals with ADHD develop bipolar disorder.
- \* Secondary mania can be produced by several medical conditions, including CVA, central nervous system (CNS) tumors, AIDS, systemic lupus erythematosus (SLE), B 12 deficiency, seizures, multiple sclerosis (MS), uremia, hyperthyroidism, and use of steroids, L-dopa, thyroxine, and antidepressants.
- \* Compliance with medication treatment increases with the half-life of the drug employed (e.g., TID dosing << BID dosing < QD dosing).



- The switch rate is 30-70% for bipolar patients receiving TCAs or MAOIs.
- Dysphoric mania predicts better anti-manic response to valproic acid than to lithium.
- Olanzapine is the only antipsychotic for which FDA approval has been granted for the treatment of mania.
- Olanzapine seems to have an antidepressant effect besides its antipsychotic properties and is very effective in the treatment for bipolar depression.
- There is as yet no clinical evidence for the efficacy of lamotrigine in acute mania.
- Combination treatment (mood stabilizer plus an antipsychotic) is more effective than monotherapy in the treatment of bipolar illness.
- Skin reactions to lamotrigine occur in about 0.1% of those who use it.
- Factors associated with lamotrigine-associated rash include an age less than 16, initial dosage, rate of titration, and concurrent use of valproate.
- The most common side effects for topiramate include dizziness, sedation, anxiety, tremor, confusion, cognitive impairment, and weight loss.
- Oxcarbazepine creates less auto-induction than does carbamazepine.
- The risk of rapid cycling is high in bipolar II patients.
- Remission is defined by a Hamilton Depression (17) score of < 7.
- A flat dose-response relationship exists for use of fluoxetine, sertraline, and paroxetine; i.e., increasing the dose is not always better.
- The dose-response relationship is unclear for bupropion (150-300 mg/day), nefazodone (300-600 mg/day), and mirtazapine (15-45 mg/day).
- An adequate time for an acute trial is 3-12 weeks.
- Most depressed patients sustain their treatment response; 70%-90% stay well within 1 year during treatment, while only 10%-20% stay well with placebo substitution.
- Depression with psychosis is best treated with an antidepressant and a neuroleptic, or with ECT.
- SSRIs with a long half-life are associated with fewer discontinuation reactions.
- Duloxetine is a new dual neurotransmitter uptake inhibitor.
- Bupropion's mechanism of action is thought to depend on both norepinephrine (NE) and dopamine (DA) uptake inhibition.
- Seizures are associated with bupropion overdose.
- Since different dyes are added to the 100 and 150-mg SR bupropion preparations, a rash with one preparation does not necessarily mean that a rash will occur with the other.

## ANTIDEPRESSANTS: CURRENT ISSUES AND NEW DRUGS

Andrew A. Nierenberg, M.D.

Dr. Nierenberg provided a comprehensive and stimulating talk on current approaches to use of antidepressant agents, and described a process by which antidepressant medications are evaluated and prescribed.

- All antidepressants are more efficacious than placebo; they are 2-3 times better than placebo for acute treatment (i.e., 4-12 weeks), and 3-4 times better than placebo for continuation (i.e., 6-12 months) and maintenance (i.e., >12 months) treatment.
- Typically, a response to an antidepressant is defined by a 50% improvement.
- Mirtazapine (Remeron) relies on alpha-2 antagonist effects and 5-HT<sub>2</sub> and 5-HT<sub>3</sub> blockade; it is also a strong antihistamine associated with increased appetite and weight gain, but no sexual dysfunction.
- Venlafaxine's mechanism of action relies on 5-HT and NE uptake inhibition. — — —
- The hypertensive effects of venlafaxine are dose-dependent.
- Trazodone, a 5-HT<sub>2</sub> antagonist and inhibitor of NE uptake, is usually prescribed in doses of 300-600 mg/day for depression; it is associated with sedation, dizziness, and priapism (1 per 6000 to 1 per 8000 cases).
- MAOIs should not be used with serotonergic agents because of risk of a serotonin syndrome; sympat-



omimetics and tyramine-containing foods should be avoided. It is important to wait at least 10 days between stopping a MAOI and starting a SSRI to give time for reconstitution of MAO.

- MAOIs are typically associated with hypotension, dizziness, insomnia, peripheral edema and when toxicity occurs, with anxiety, confusion, seizures, tachycardia, hallucinations, and hypertensive crisis.
- Reboxetine is a NE uptake inhibitor, prescribed in 2-4 mg doses; it has a half-life of 13 hours (and it is renally excreted).
- Reboxetine's side effects include dry mouth, constipation, sweating, insomnia, tachycardia, headache, blood pressure changes, and sexual dysfunction.
- St. John's Wort (*Hypericum*) is used in doses of 300-mg tid; its mechanism of action is unclear.
- Lamotrigine is completely absorbed after oral ingestion and it is 94% renally excreted. While its half-life when taken alone is 25-33 hours, when taken with carbamazepine its half-life decreases to 12-15 hours; with valproic acid, the half-life increases to 48-70 hours.
- Routine monitoring of laboratory values is not required when taking lamotrigine. However, side effects include headache, ataxia, nausea, and sedation.
- There is some evidence that dual action antidepressants are better than selective agents for treatment of the severely ill.
- SSRIs are more effective than is bupropion in the treatment of irritable depression.
- Bupropion does not cause sexual dysfunction or weight gain.

## STRATEGIES IN THE TREATMENT OF REFRACTORY DEPRESSION: DOSE INCREASE AND SWITCHING

Maurizio Fava, M.D.

Dr. Fava, a leading researcher into the treatment of refractory depression provided a data-filled presentation on the state-of-the-art in medication management and he offered substantial amounts of practical advice.

- 29% to 46% of patients with depression have a partial response or have no response to antidepressants.

- Partial response to antidepressants is defined as a 25%-49% reduction in symptoms.
- Among responders to antidepressants, residual symptoms are common.
- Studies of treatment-resistant depression are hampered by the heterogeneity of populations studied, by misclassification of relapsers as non-responders, by use of retrospective (rather than prospective) studies, and by open (rather than controlled) studies.
- Treatment strategies for treatment-resistant depression include dose increases, switches to another agent, augmentation, and use of combination therapies.
- Disadvantages of dose increases include higher costs, a greater propensity for side effects, and for some agents, a need for blood or ECG monitoring.
- The first-choice strategy for partial responders to eight weeks of SSRI therapy is a dose increase of the SSRI.
- A frequently followed rule with dose increases is "if there are no side effects, consider increasing the dose further."
- Approximately 25% of patients started on an SSRI are switched to another antidepressant during treatment.
- After non-response to an SSRI, many clinicians switch to another SSRI (because of differences within a class) or to a non-SSRI agent (to obtain a different neurochemical effect).
- Switching is often viewed as a more acceptable strategy than is the addition of another agent (polypharmacy).
- Switching may result in different (but not better) side effects.
- When switching from one antidepressant to another the first agent should be gradually tapered while starting the new one.
- Psychiatric co-morbidity is a contributing factor to treatment resistant depression.
- An immediate switch from one SSRI to another appears to be well tolerated without a taper.
- Switching to mirtazapine may prevent SSRI discontinuation reactions by blocking 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors.

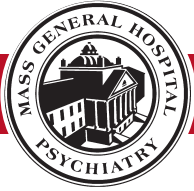


## STRATEGIES IN THE TREATMENT OF REFRACTORY DEPRESSION: AUGMENTATION AND COMBINATION

Jerrold F. Rosenbaum, M.D.

Dr. Rosenbaum eloquently reviewed the phases of antidepressant treatment and outlined the therapeutic options regarding treatment-resistant depression. He described a variety of augmentation strategies and discussed what clinicians do when sub-optimal responses of SSRIs have been obtained.

- Treatment options when treatment resistance occurs include optimization of antidepressant treatment (e.g., raising the dose, extending the duration of use, addressing compliance issues, minimizing and managing adverse effects, and optimizing plasma levels), augmentation with another pharmacological agent, and switching from one antidepressant to another (with a different receptor profile or with superior efficacy).
- The STAR-D (Sequential Treatment Alternatives to Relieve Depression) trial is a five-year study whose aim is to develop and evaluate clinical strategies to improve outcomes for patients with treatment-resistant depression.
- The STAR-D trial hopes to identify best “next-step” treatments for depressed patients who fail to respond satisfactorily to earlier treatment attempts and to compare relative efficacy and patients’ acceptance of different treatment strategies.
- The goals of antidepressant treatment are symptom reduction (remission), relapse prevention, recurrence prevention, and restoration of function.
- 60%-80% of patients with major depressive disorder (MDD) in clinical trials respond to antidepressants when response is defined as a 50% decrease in Hamilton-Depression (HAM-D) scores.
- Remission of depressive symptoms is the goal of antidepressant treatment, i.e., not meeting criteria for MDD and having a HAM-D of < 7 for > 3 weeks.
- < 50% of patients with MDD remit with a single adequate antidepressant trial.
- 10%-25% of patients with MDD suffer a relapse in the first year, despite continued antidepressant treatment.
- 50%-85% of patients with MDD will suffer recurrences.
- Treatment resistance is the failure to achieve and sustain euthymia despite an adequate antidepressant treatment.
- Treatment resistance may be the result of misdiagnosis, psychiatric co-morbidity, medical causes of co-morbidity, treatment-emergent adverse effects, noncompliance, and social adversity.
- Risk factors for relapse and recurrence include multiple prior episodes, a long duration of an index episode, double depression, presence of residual symptoms, an older age of onset, and co-morbidity.
- Bupropion is often preferred as a popular augmentation strategy for SSRI-induced apathy, sexual dysfunction, and sub-optimal response.
- In general, clinicians raise the dose of an antidepressant with partial responders, switch to a non-SSRI agent for non-responders, and raise the dose for those who relapse.
- Modafinil is a new agent for excessive daytime somnolence and narcolepsy with minimal abuse potential at therapeutic doses.
- Olanzapine has been observed to improve depressive symptoms in those with schizophrenia.
- Mirtazapine improves sleep and sexual dysfunction in depressed patients, and is presumed to work via its action as an alpha-2 antagonist.
- Pramipexole is a dopamine agonist (indicated for Parkinson’s disease) with affinity for D3, D2, and D4 receptors; its main side effects are nausea and hypotension, which are minimized by slow titration.
- Thyroid hormone has been reported to accelerate response or to treat non-responders.
- Pindolol, a beta-blocker with 5-HT1A antagonist effects, has shown a slight acceleration of an initial response, but not an enhancement of response in non-responders.
- Lamotrigine may have some efficacy in bipolar disorder, but it is less effective in unipolar conditions.
- Light therapy and sleep deprivation are examples of non-pharmacological treatments for subtypes of treatment-resistant depression.
- Bupropion added to an SSRI in a combination strategy has addressed SSRI induced apathy, sexual dysfunction, and sub-optimal response.
- Combining bupropion with SSRIs appears to be safe in moderate doses of 150-300 mg.



## LIABILITY PREVENTION IN PSYCHOPHARMACOLOGY

Ronald Schouten, M.D., J.D.

Dr. Schouten, trained both as a psychiatrist and as an attorney, succinctly defined and explained commonly used terms related to forensic psychiatry and guided the audience to an understanding of liability issues related to the practice of psychopharmacology.

- Since 1990, the majority of malpractice claims have shifted from the inpatient realm to the outpatient setting.
- Among CRICO's medication-related malpractice claims, >60% of alleged errors were associated with 5 drug groups: antibiotics, anticoagulants, steroids, narcotics, and cardiovascular drugs.
- Risk factors for malpractice claims include miscalculation of dosage relative to a patient's weight, medications being prescribed prior to reaching a diagnosis, lack of clinician knowledge about drug side effects, drug-drug interactions, and drug-disease interactions, clinicians not being immediately available in the event of complications at home, clinicians disregarding known warning signs, failure to tell patients to discontinue the drugs once side effects were noted, dismissing multiple toxic side effects as common side effects, failure to counsel patients on the intended effects of treatment so that they'll be better able to detect an unintended effect, and failure to coordinate simultaneous treatment with multiple providers.
- Inadequate monitoring, prescribing the wrong dose, and improperly managing a medication regimen account for > 50% of medication-related malpractice claims.
- A general rule in medico-legal contexts is "if it's not written down, it probably didn't happen."
- Malpractice claims tend to be associated with a bad outcome and bad feelings.
- A tort is a civil wrong giving rise to the right to sue for damages.
- Assault is an intentional, unlawful threat of physical injury directed to another person where that person has a well-founded belief that injury may occur.
- Battery is the intentional touching of another without their consent and without justification; contact has to occur.
- For malpractice to be found, the "4 D's " must be present: a Dereliction of a Duty, which Directly causes Damages.
- The most common allegations of psychiatric malpractice are improper diagnosis and/or treatment; violation of rights; inadequate monitoring; sexual misconduct; medication-related adverse outcomes; and failure to ensure safety.
- Abandonment is the unilateral and unjustified termination of a doctor-patient relationship by the physician without reasonable notice, which leaves the patient without treatment; this becomes actionable if injury results.
- Informed consent is a process by which one individual agrees to allow another individual to intrude upon their bodily integrity or other rights where the agreeing party is competent to consent and the consent is given voluntarily and with a reasonable degree of knowledge of the factual situation.
- In the professional standard of informed consent, the amount of information provided is that which the reasonable medical practitioner would provide under the same circumstances.
- The materiality standard of informed consent provides the information that the average patient would require to make a decision under the same circumstances.
- When determining competency, one should establish if the patient evidences a choice, is able to understand the relevant information, is able to appreciate the seriousness of the condition and the consequences of accepting or rejecting treatment, and is able to manipulate the information provided in a rational fashion.
- Exceptions to requiring informed consent include emergency situations, where a waiver is present, and when there is therapeutic privilege.
- Confidentiality is the duty of a professional to keep matters revealed in confidence from third parties.
- Exceptions to confidentiality include emergencies, waivers, incompetence, commitment, statutory reporting requirements, statutory exceptions (e.g., malpractice allegations), and the duty to protect third parties.
- All competent individuals have a right to make decisions concerning their own medical treatment even though the decision may be at odds with the decision of their physician.



cian or with what a majority of others might choose under the same circumstances.

- \* In a forensic evaluation the client is the attorney, court or agency, and the patient is not; confidentiality is absent.
- \* Malpractice in psychopharmacology often involves misdiagnosis, failure to treat, and negligent treatment.

## PHARMACOTHERAPY OF OBSESSIVE COMPULSIVE DISORDERS

Michael A. Jenike, M.D.

In a comprehensive lecture, Dr. Jenike treated the audience to a bevy of facts about Obsessive-Compulsive Disorder (OCD) and its related disorders. He laced the presentation with humorous vignettes that highlighted the clinical issues.

- \* The prevalence of OCD is 2%-3% of the US population.
- \* Medications and Cognitive-Behavioral Therapy (CBT) are the two primary treatments for OCD.
- \* Drugs found partially successful for OCD are clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram.
- \* OCD generally responds to SSRIs used in higher doses than are used for depressive disorders.
- \* Augmenting agents (added to an antidepressant to improve response) include clonazepam, lithium, buspirone, trazodone, methylphenidate, and neuroleptics (if the OCD patient has tics).
- \* The behavioral techniques found useful for the treatment of OCD are exposure and response prevention.
- \* OCD is a chronic illness; it is rarely cured.
- \* The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is a 10-item scale that assesses the severity of OCD.
- \* The diagnosis of OCD requires either obsessions or compulsions, which cause significant distress or interferes with social or role functioning.
- \* Two-thirds of OCD patients develop major depression during their lifetime.
- \* For cases of severe OCD, several neurosurgical techniques (i.e., subcaudate tractotomy, cingulotomy, limbic leucotomy, and anterior capsulotomy) have been employed.

## PHARMACOLOGICAL MANAGEMENT OF COGNITIVE AND BEHAVIORAL DISORDER IN ALZHEIMER'S DISEASE

Gary L. Gottlieb, M.D., M.B.A.

Dr. Gottlieb eloquently reviewed the characteristic features of a variety of dementing illnesses and discussed methods to screen for, and manage these disorders. In addition, the diagnosis and treatment of depression, agitation, psychosis, and anxiety, in those with dementia were discussed.

- \* Dementia affects roughly 8% of those greater than 65 years old.
- \* AD accounts for two-thirds or more of all dementia cases.
- \* Beginning at age 60, the prevalence of AD doubles every five years.
- \* The APOE-4 allele increases the likelihood of developing AD and decreases the age at onset.
- \* Age is the strongest risk factor for AD, but a positive family history of AD, and a history of head trauma may also be significant.
- \* Vascular dementia accounts for 15% of all dementia cases.
- \* Pathologic changes detected in the brains of individuals with AD include the presence of neurofibrillary tangles, neuritic plaques, and amyloid in the neuropil.
- \* Cholinesterase inhibitors are the only class of drug proven to enhance cognitive function.
- \* Tacrine [Cognex], a reversible cholinesterase inhibitor is associated with mild, transient vomiting and/or nausea in 30% of cases and is associated with an elevation of liver enzymes; monitoring of liver function is necessary before administration and throughout dose titration.
- \* Donepezil is a reversible cholinesterase inhibitor, not associated with hepatotoxicity; more cholinergic side effects are reported at doses of 10 mg/day.
- \* Options under investigation for treatment of cognitive decline associated with dementing illnesses include Aricept (donepezil), Exelon (rivastigmine), Cognex (tacrine), vitamin E (alpha-tocopherol), NSAIDs, estrogen, Ginkgo biloba, neutropil growth factor, and Eldapryl (selegiline).



- \* Vascular dementia, in general, presents and progresses in a slow, stuttering, stepwise manner.
- \* Diffuse Lewy Body Disease (DLBD) typically presents with more movement disorders and hallucinations than does AD.
- \* Frontal lobe dementias tend to present with prominent personality changes (e.g., indifference, and disinhibition) and behavioral changes (e.g., a loss of personal or social awareness and stereotyped behaviors).
- \* More than 50% of patients with reversible dementia and major depression will develop irreversible dementia within five years.
- \* Nearly half of AD patients have clinically significant depressive symptomatology; nearly a quarter meets criteria for major depression.
- \* Psychosis, agitation, and aggression in AD patients are the most troubling behaviors for caregivers, and are the most frequent cause of institutionalization and specialist referral.
- \* Antipsychotics are most commonly started in the evenings to foster sleep and minimize behavioral problems that worsen in the evening (sundowning).
- \* Use of atypical antipsychotics is associated with a very low risk of tardive dyskinesia in the elderly.
- \* Benzodiazepines are not typically useful for treating agitation in demented individuals.
- \* Early features of AD include cognitive impairment (e.g., memory loss [especially for recent events], language difficulties [aphasias], and visuospatial dysfunction); functional losses (e.g., social and occupational activities, learned motor activities, and instrumental activities of daily living [IADLs]); and behavioral and mood changes (e.g., apathy, irritability, anxiety, and depression).
- \* Mutations on chromosomes 1, 14, and 21 cause early-onset familial forms of AD.
- \* Patients with dementia with Lewy bodies are more sensitive to the extrapyramidal effects of antipsychotic medications.
- \* Risk factors for AD include advanced age, family history of AD, apolipoprotein 4, and Down's syndrome.

## DRUG-DRUG INTERACTIONS

Jonathan E. Alpert, M.D., Ph.D.

Dr. Alpert's encyclopedic presentation described pharmacodynamic interactions and pharmacokinetic interactions, and identified a dozen interactions that are essential for practitioners to know about. A bevy of useful figures and tables were also presented.

- \* Drug interactions are alterations in drug plasma levels, tissue concentrations, and/or drug effects associated with the use of two or more prescribed, illicit, or over-the-counter agents in close temporal proximity.
- \* Psychotropic drug interactions rarely imply contraindications to concurrent use.
- \* Factors that contribute to inter-individual variability in drug levels and treatment responses include age, gender, nutritional status, smoking and alcohol consumption, disease states altering hepatic and renal clearance, genetic polymorphisms, and compliance with recommended dosing.
- \* Some drug interactions are "friendly"; i.e., they can manage drug-related nausea, reverse drug overdoses, prolong drug actions, and enhance levels of costly drugs.
- \* Pharmacodynamic effects are alterations in pharmacological effects either produced directly by agonist or antagonist interactions at a common receptor site, or indirectly, at separate but interrelated biological sites.
- \* Pharmacokinetic effects are alterations in plasma levels and or tissue concentrations produced by interactions that affect drug absorption, distribution, metabolism, or excretion.
- \* Pharmacodynamic effects include respiratory depression (from benzodiazepines), prolongation of the QTc (with TCAs, or antipsychotics), anticholinergic symptoms (from diphenhydramine or clozapine), or hypotension (from TCAs, MAOIs, or trazodone).
- \* Anticholinergic toxicity can be caused by the interactions between TCAs. Low potency antipsychotics, clozapine, olanzapine, diphenhydramine, benztropine, paroxetine, and mirtazapine.
- \* Some drugs have a therapeutic window, others have a low therapeutic index, while still others have the potential for catastrophic side effects.



- \* One Internet resource for information about drugs is : [www.drug-interactions.com](http://www.drug-interactions.com).
- \* Charcoal, antacids, and kaolin-pectin may bind to drug and form unabsorbable complexes.
- \* Drugs that speed gastric emptying (e.g., metoclopramide and cisapride [Propulsid]) or inhibit intestinal motility (e.g., TCAs, morphine, and marijuana) may promote greater contact with absorptive mucosal surfaces of the upper portion of the small intestine.
- \* Cachexia and liver failure typically reduce serum protein levels, potentially increasing risk of protein-binding interactions.
- \* Protein-binding interactions are often inconsequential except when drugs are highly bound and have a low therapeutic index.
- \* Most psychotropics are extensively protein bound; exceptions are lithium (<3%), gabapentin [Neurontin] (<3%), topiramate [Topamax] (<20%), and venlafaxine [Effexor] (<30%).
- \* Inhibition is typically associated with a rapid impact (within hours to days) on blood levels of a relevant coadministered drug. Common inhibitors include antifungals, antiretrovirals, Isoniazid, antimalarials, SSRIs, phenothiazines, valproic acid, psychostimulants, beta-blockers, amiodarone, mexilitene, cimetidine, quinidine, calcium channel blockers, disulfiram, and grapefruit juice.
- \* Induction is associated with a more gradual effect, over days to weeks (via enhanced synthesis of an enzyme). Common inducers include carbamazepine, phenobarbital, phenytoin, primidone (Myosoline), cruciferous vegetables, ritonavir, cigarette smoking, rifampin, char-broiled meats, and St. John's Wort.
- \* The nomenclature of the cytochrome P450 isoenzyme system identifies the family, the subfamily, and the individual isoenzyme of a drug. For example: P450 1A2; P450 = pigment absorbing light at 450 nm, 1 = family, A = subfamily, and 2 = individual isoenzyme.
- \* Of the P450 isoenzymes, the most relevant to drug metabolism and interactions are 3A, 2D6 (a gene on chromosome 22), 1A2, and 2C subfamilies.
- \* 5%-10% of Caucasians and 1%-3% of African and Asian Americans are poor metabolizers of P450 2D6 metabolites.
- \* Drugs can be metabolized by more than one enzyme system.
- \* Co-administration of MAOIs and sympathomimetics may lead to a hypertensive crisis.
- \* Use of MAOIs and meperidine may result in a serotonin syndrome.
- \* Signs and symptoms of serotonin syndrome include mental status changes, agitation, myoclonus, clumsiness, hyperreflexia, tremor, fever, shivering, diaphoresis, and diarrhea.
- \* Carbamazepine is a potent inducer of metabolism (reducing levels and efficacy) of many psychotropics of all classes, via induction of P450 3A isoenzymes.
- \* P450 2D6 inhibition by SSRIs, bupropion, and phenothiazines will elevate levels of 2D6 substrates, including TCAs, beta-blockers, and antiarrhythmics.
- \* P450 3A inhibition by nefazodone and fluvoxamine can increase levels of carbamazepine, cyclosporine, alprazolam, zolpidem, calcium channel blockers, and pimozone, among others.
- \* Use of St. John's wort may reduce the efficacy of cyclosporine and birth control pills.
- \* P450 inhibition by fluvoxamine can lead to toxicity of clozapine and theophylline.
- \* Lithium levels will increase with use of thiazides, NSAIDs, ACE inhibitors, and some antimicrobials.
- \* Lithium levels will decrease with use of aminophylline, osmotic diuretics, and sodium chloride.
- \* Inhibition of metabolism by valproate or lamotrigine may elevate the carbamazepine 10,11-epoxide metabolite and increase the risk of toxicity.
- \* MAOIs should not be initiated until 5 weeks after discontinuation of fluoxetine.
- \* Mirtazapine is a potent antagonist of the alpha-adrenergic receptor as well as a potent antagonist at the histamine receptor and a moderate antagonist at the muscarinic receptor.
- \* Many drug interactions, like treatment of side effects (e.g., use of anticholinergics for EPS and 5-HT3 blockade for nausea) are desirable.
- \* Idiosyncratic drug interactions are sporadic interactions that occur in a small number of individuals and which are not predicted from known pharmacodynamic or pharmacokinetic properties of the drugs.



- Pharmacodynamic interactions are produced directly at a common biological site (receptor) (e.g., clonidine and yohimbine competing for the same alpha-adrenergic receptor site).
- Marijuana, morphine, and TCAs inhibit intestinal motility that increases the rate of absorption of other drugs.
- Most psychotropic drugs are extensively protein-bound.
- Minimal protein bound psychotropics include lithium, gabapentin, topiramate, and venlafaxine.
- Metabolic inhibition causes a rapid impact on drug interactions, whereas metabolic induction has a gradual impact on serum drug levels.
- SSRIs when used in combination with MAOIs are contraindicated; their co-administration can cause serotonin syndrome.

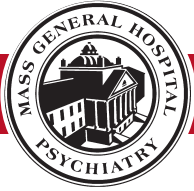
- Selective serotonin reuptake inhibitors (SSRIs) (which include fluoxetine [Prozac], sertraline [Zoloft], paroxetine [Paxil], fluvoxamine [Luvox], and citalopram [Celexa]) are more efficacious than tricyclic antidepressants (TCAs) in the treatment of social phobia.
- Side effects associated with SSRIs include GI distress, jitteriness, headaches, sleep disturbances, and sexual dysfunction.
- Discontinuation of treatment for anxiety disorders can be met with withdrawal reactions or relapse.
- Patients with posttraumatic stress disorder (PTSD) have experienced an event that involved the threat of death, injury, or severe harm to themselves or others; their response involves intense fear, helplessness, or horror.
- Patients with PTSD frequently re-experience the traumatic event with nightmares, flashbacks, or marked arousal, when exposed to situations reminiscent of the event.
- Nocturnal flashbacks and nightmares in PTSD seem to respond to valproate, carbamazepine, gabapentin, topiramate, and lamotrigine.
- The prevalence of generalized anxiety disorder (GAD) in community samples is 5%, with a female: male ratio of 2:1; it typically begins in childhood or adolescence.
- GAD is often treated with antidepressants.
- Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, is indicated for GAD, and is effective for panic disorder, OCD, social phobia, and PTSD.
- Symptoms of GAD include persistent anxiety and worry, occurring more days than not for at least six months, about a number of events or activities.
- Ninety percent of patients with GAD have a co-morbid psychiatric disorder; most commonly this disorder is depression.
- Pharmacotherapy of anxiety disorders includes use of TCAs, SSRIs, benzodiazepines, monoamine oxidase inhibitors (MAOIs), buspirone, and beta-blockers.
- Typical side effects of TCAs include anticholinergic effects (dry mouth, blurred vision, constipation, tachycardia), orthostatic hypotension, weight gain, cardiac conduction system disturbances, and sexual dysfunction.
- MAOIs, including phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxacid (Marplan), are associated

## THE DRUG TREATMENT OF ANXIETY, PANIC ATTACKS, AND PHOBIAS

Mark H. Pollack, M.D.

Dr. Pollack provided a well-rounded overview of the spectrum of anxiety disorders (covering diagnostic criteria, prevalence, and treatment); he punctuated his discussion with examples of his dry sense of humor.

- Anxiety disorders are among the most prevalent psychiatric disorders in the general population.
- First-degree relatives of patients with anxiety disorders have a significantly increased risk for anxiety disorders compared with those in the general population.
- The lifetime prevalence of any anxiety disorder in the US is 24.9%; for panic disorder it is 1.5-3.5%, with a female: male ratio of 3:1.
- Panic disorder is a syndrome characterized by recurrent unexpected panic attacks about which there is persistent concern.
- Patients with social phobia fear being exposed to public scrutiny; they fear that they will behave in a manner that will be humiliating or embarrassing.
- The lifetime prevalence of social phobia has been estimated to be 3-13%.
- Gabapentin has been shown to be effective in the treatment of social phobia.



with weight gain, orthostatic hypotension, sexual dysfunction, and the potential for hypertensive crises with dietary indiscretions (tyramine-containing foods) or stimulatory mediations.

- Clonazepam is thought to be twice as potent as is alprazolam; each is effective for panic disorder.
- Beta-blockers decrease signs of autonomic arousal and are useful as adjuncts for somatic symptoms of panic disorder and GAD (but not as a primary treatment).
- Initial doses of SSRIs for anxiety should be lower than the lower end of the usual dosage range.
- The usual dosage range of SSRIs for anxiety disorders includes: fluoxetine, 20-80 mg/day; sertraline, 50-200 mg/day; paroxetine, 20-50 mg/day; fluvoxamine, 100-300 mg/day; citalopram, 20-60 mg/day; venlafaxine, 75-300 mg/day; and nefazodone, 300-500 mg/day.
- Buspirone is a non-benzodiazepine anxiolytic indicated for use in GAD.
- Withdrawal and rebound are more commonly associated with benzodiazepines than they are with other anti-panic treatments (e.g., SSRIs).
- Strategies for discontinuation of anxiolytics include a slow taper, a switch to a longer-acting agent for the taper, cognitive-behavioral therapy (CBT), and the use of adjunctive agents (e.g., antidepressants, anticonvulsants, clonidine, beta-blockers, or buspirone).
- Dose equivalents (mg) for benzodiazepines are: oxazepam (15 mg); alprazolam (0.5 mg); chlordiazepoxide (10 mg); clonazepam (0.25 mg); diazepam (5 mg); flurazepam (5 mg); clorazepate (7.5 mg); and midazolam (2 mg).
- SSRIs should be started at a low dose to minimize anxiety when treating an anxiety disorder; however, pushing the dose higher seems to produce better efficacy.
- Benzodiazepines can be used in a p.r.n. basis for situational anxiety.
- Combining an antidepressant with a benzodiazepine can decrease early anxiety associated with initiation of an antidepressant. However, after 4-5 weeks the benzodiazepine should in general be tapered.

## THE ART OF MANAGING SIDE EFFECTS

Mark H. Pollack, M.D.

Dr. Pollack continued his discussion of psychopharmacologic management with a comprehensive review of adverse effects associated with antidepressant medications.

- Management of side effects allows enhanced compliance, permits adequate dosing, and prevents premature stoppage of treatment.
- Anticipation of problematic side effects and usage of the lowest effective dose improves compliance.
- Antidepressant-induced side effects include sexual dysfunction, CNS effects, weight gain, gastrointestinal distress, orthostatic hypotension (OH), and anticholinergic effects.
- Categories of sexual dysfunction include decreases in libido, erectile dysfunction, delayed ejaculation, and inhibited orgasm.
- 30% to 40% of individuals on SSRIs develop sexual dysfunction.
- Pharmacological treatments for antidepressant-induced sexual dysfunction include: sildenafil (Viagra) at 50-100 mg 30 - 60 minutes before sexual relations; yohimbine (2.7-5.4 mg qd-tid); bupropion (75-150 mg/day); amantadine (100 mg bid-tid); and cyproheptadine.
- Jitteriness and tremor induced by antidepressants may be alleviated by use of a beta-blocker or benzodiazepines.
- Paresthesias may result from MAOI-induced pyridoxine deficiency; they may be treated by administration of pyridoxine, 50-150 mg/day.
- Fatigue may be managed by switching a sedating agent to bedtime dosing, by lowering the dose of the offending agent, by addition of caffeine, or modafinil (Provigil), or a stimulant.
- Trazodone and mirtazapine appear to be effective for disturbances of sleep induced by SSRIs.
- Cognitive slowing may benefit from caffeine, doxepin, modafinil, or a stimulant.
- Weight gain is associated with antihistamine potency of antidepressants; potencies for the histamine H1 receptor are as follows: doxepin > trimipramine > amitriptyline > maprotiline > nortriptyline > amoxapine > clomipramine > desipramine > trazodone > fluoxetine >



bupropion > paroxetine > nefazodone > sertraline > fluvoxamine > venlafaxine.

- \* Management of weight gain may benefit from minimization of antihistaminic agents, by diet and exercise, by avoidance of sugared beverages to treat dry mouth, and by use of diuretics to reduce edema. In addition, modafinil, stimulants, and thyroid supplementation have been used with success.
- \* OH is associated with affinities for the alpha 1 adrenergic receptor; potencies of antidepressants at the alpha 1 adrenergic receptor are as follows: doxepin > trimipramine > trazodone > clomipramine > nefazodone > amoxapine > nortriptyline > maprotiline > imipramine > protriptyline > desipramine > sertraline > paroxetine > bupropion > fluoxetine > fluvoxamine > venlafaxine.
- \* OH can be managed by correction of dehydration, adjustment of antihypertensive agents, rising slowly from the recumbent position, use of support hose, administration of caffeine, T3, flonidol (0.05-0.5 mg/day), and salt tablets (600-1800 mg/day).
- \* Anticholinergic effects of antidepressants are associated with their affinities for muscarinic receptors; their potencies are as follows: amitriptyline > protriptyline > clomipramine > trimipramine > doxepin > imipramine > paroxetine > nortriptyline > desipramine > maprotiline > sertraline > amoxapine > fluoxetine > nefazodone > fluvoxamine > bupropion > trazodone > venlafaxine.
- \* Dry mouth induced by antidepressants can be treated/managed by sugarless gum, artificial saliva preparations, a 1% pilocarpine rinse, bethanacol (10-30 mg qd-tid), or yohimbine (2.5-15 mg/day).
- \* Lithium-induced polyuria can be managed with hydrochlorothiazide or amiloride, while lithium-induced tremor may benefit from a reduction in dosage, use of a beta-blocker, or a benzodiazepine.
- \* Any psychotropic that raises serotonin can inhibit sexual function; drugs that raise the dopamine level may enhance sexual function.
- \* Benzodiazepines are effective in the treatment of jitteriness and tremor.
- \* Modafinil is useful in the treatment of fatigue and sedation associated with SSRIs.
- \* Topiramate, in doses of 25-400 mg/d, can be titrated against sedation and cognitive impairment for treatment of weight gain secondary to use of atypical antipsychotics and antidepressants.

## INTEGRATING COGNITIVE-BEHAVIORAL THERAPY WITHIN PHARMACOTHERAPY: A FOCUS ON ANXIETY

Michael W. Otto, Ph.D.

Dr. Otto delivered an energetic and well-organized presentation on the theory and practical application of CBT to the management of anxiety syndromes. He highlighted the principles presented with clinical vignettes.

- \* Cognitive-behavioral therapy (CBT) has been shown to be an effective alternative to, and adjunctive treatment to medication for anxiety disorders.
- \* Combination treatment (CBT and pharmacotherapy) results in a greater acute response to treatment and in greater maintenance treatment gains.
- \* CBT targets maladaptive chains of thought, feelings, and behaviors.
- \* The core fears associated with anxiety disorders can be approached. For panic disorder they are fears of anxiety sensations; for social phobia they are fears of negative evaluations; for OCD they are fears of perceived catastrophes; for PTSD they are fears of traumatic memories; and for GAD they are chronic worries.
- \* Elements of CBT include provision of information, exposure to the feared stimulus, cognitive restructuring, and symptom-management skills training.
- \* Relaxation training and breathing retraining are techniques that facilitate anxiety relief.
- \* One step in CBT is to break the chain of the anxiety experience into understandable elements.
- \* CBT provides a model for change.
- \* Cognitive restructuring allows for a substitution of more accurate and useful thoughts.
- \* Exposure to a feared situation is often repeated until fear diminishes in CBT.
- \* Use of safety behaviors impairs anxiety reduction in patients with social phobia.
- \* The use of stories and metaphors in CBT provides a method to enhance information processing in sessions and thereafter.
- \* CBT should be reapplied when discontinuing medication.
- \* Sequential addition of CBT improves treatment outcome for medication non-responders or for partial responders.



## JUVENILE MOOD DISORDERS

Jeff Q. Bostic, M.D., Ed.D.

Dr. Bostic described the clinical presentation of juvenile mania and reviewed the treatment approach to afflicted individuals in detail. Irritability, prolonged outbursts, affective storms, and an overlap with ADHD are the rule; he also comprehensively described recent research in the field of childhood and adolescent mania and noted that juvenile mania is not as rare as previously thought. Juvenile mood disorders are often confused with severe ADHD, because of overlapping symptoms. Treatment, with lithium, valproate, carbamazepine, Lamictal, and atypical neuroleptics, are often effective for juvenile mood disorders.

- \* The age of onset of juvenile mania is often different from the age of its recognition.
- \* Juvenile bipolar disorder is estimated to affect 5% of children.
- \* A rapid onset, psychomotor retardation, a family history of bipolar disorder, and a switch to mania induced by antidepressants facilitate the diagnosis of bipolar disorder.
- \* Irritability, persistent outbursts, and violent behaviors, such as attacking family members, are also key in the detection of bipolar disorder.
- \* Adolescent mania is associated with an increased number of suicide attempts.
- \* Rather than present with euphoria, manic children are more likely to be irritable with affective storms or prolonged and aggressive temper outbursts.
- \* Outbursts often involve threats or attacking behavior towards others, including family members, other children, adults, and teachers.
- \* Symptoms (e.g., distractibility, hyperactivity, and talkativeness) of mania overlap with manifestations of ADHD.
- \* Grandiosity in juvenile mania may present as extreme defiance and oppositionality.
- \* Bipolar disorder is a strong risk factor for substance abuse.
- \* Treatments for mania do not treat ADHD.
- \* Treatment-resistant children and adolescents with depression may suffer from unrecognized bipolar disorder.

- \* Children with bipolar disorder present with an insidious onset, severe irritability, chronicity and mixed symptoms with major depression.

- \* To prevent manic relapse, SSRIs should in general not be added until after mood stabilizers are in place.

## OBSESSIVE COMPULSIVE SPECTRUM DISORDERS

Darin Dougherty, M.D.

Dr. Dougherty treated the audience to a comprehensive treatise on OCD spectrum disorders. He reviewed the differential diagnosis for, and the phenomenology, prevalence, and treatment of a variety of conditions.

- \* Obsessive-compulsive spectrum disorders include trichotillomania, body dysmorphic disorder, Tourette's disorder, psychogenic excoriation, pathological gambling, kleptomania, pyromania, compulsive shopping, Internet addiction, sex addiction, and possible eating disorders.
- \* A genetic component exists for all obsessive-compulsive spectrum disorders.
- \* Co-morbidity for obsessive-compulsive spectrum disorders is frequent.
- \* Up to one-fourth of individuals with trichotillomania and nearly one-third of those with OCD have body dysmorphic disorder.
- \* One-fourth to one-half of patients with Tourette's disorder also has OCD.
- \* Sufferers from obsessive-compulsive spectrum disorders also have a higher rate of major depression, social phobia, and substance abuse than those in the general population.
- \* Trichotillomania involves recurrent hair pulling with hair loss; tension develops before hair-pulling and is relieved when pulling out hair.
- \* Roughly one-third of the time hair is pulled from one site; two-thirds of the time two or more sites are involved in trichotillomania. The scalp, eyelashes, and eyebrows are the most common sites.
- \* More than two-thirds of those with trichotillomania are female.



- \* Complications of trichotillomania include alopecia, infections, trichobezoars, carpal tunnel syndrome, and low self-esteem.
- \* Body dysmorphic disorder (BDD) involves a preoccupation with an imagined defect in appearance in a normal-appearing person or markedly excessive concern about a slight imperfection.
- \* The focus of concern in BDD is often the head and face, though any body part may be the focus of concern.
- \* Sequelae of BDD include avoidance and isolation, self-mutilation, and remaining unmarried; nearly 75% of BDD patients have never been married.
- \* Behavioral therapy for BDD includes exposure and response prevention, as well as removing mirrors, limiting grooming time, and not using make-up.
- \* Pharmacotherapy of trichotillomania and BDD includes use of SSRIs, as well as other antidepressants, mood stabilizers, neuroleptics, naltrexone, and topical steroids.
- \* Multiple motor tics and/or one or more vocal tics occur many times per day in Tourette's disorder.
- \* Tics of Tourette's disorder are involuntary, though they may be suppressed.
- \* Patients with Tourette's disorder have higher rates of attentional dysfunction, learning disability, and failure to inhibit aggressive or self-injurious behavior.
- \* Behavioral therapy for Tourette's disorder involves relaxation techniques, habit reversal, isometric muscle tensing to oppose tics, and tic substitutions.
- \* Pharmacotherapy of Tourette's disorder includes use of neuroleptics, clonidine, TCAs, SSRIs, and stimulants.
- \* Other behaviors related to trichotillomania include nail biting, tongue chewing, head banging, cheek chewing, and skin picking.
- \* One-fourth of trichotillomania patients also have body dysmorphic disorder.
- \* SSRIs are the first-line treatment for trichotillomania and BDD.
- \* The most common co-morbid disorders with Tourette's are ADHD, learning disabilities, and OCD.

## THE COURSE AND TREATMENT OF PSYCHIATRIC ILLNESS IN PREGNANCY

Lee S. Cohen, M.D.

Dr. Cohen, a prolific investigator of psychiatric disorders and their treatment during pregnancy and the postpartum period, presented a fact-filled discourse on the natural history and treatment of mood disorders in pregnancy.

- \* No decision regarding the use of psychotropics in the peripartum period is risk free; drugs are employed when the risk to the mother and fetus from the disorder outweighs the risks of pharmacotherapy.
- \* When deciding on whether to maintain or discontinue antidepressant treatment during pregnancy, consider the maternal illness history, the patient's wishes, and available safety data. Also consider the risk of relapse and the risk of an untreated disorder.
- \* 50% of pregnancies in this country are unplanned, making the use of psychotropics in women of childbearing age a notable public health issue.
- \* There does not appear to be an increased risk for major congenital malformations following either first-trimester exposure to TCAs or fluoxetine.
- \* Although less information is available on newer antidepressants (e.g., sertraline, paroxetine, venlafaxine, citalopram, nefazodone, mirtazapine, fluvoxamine, and bupropion) during pregnancy, no evidence yet suggests an increased rate of major malformations.
- \* Data show that obstetrical complications and poor neonatal outcome occur more commonly in depressed pregnant women.
- \* Data support the safety of typical antipsychotics during pregnancy.
- \* Many clinicians recommend avoiding a change in antidepressant therapy during pregnancy, consistent with the southern expression, "dance with the one that brung ya."
- \* Use of lithium during the first trimester is associated with an increased risk of the cardiac malformation, Ebstein's anomaly (1/1000-1/2000).
- \* Carbamazepine use during the first trimester is associated with a 0.5%-1% risk of spina bifida, craniofacial abnormalities, microcephaly, and growth retardation.



- \* Valproic acid use during the first trimester is associated with a 3%-6% risk of spina bifida, craniofacial abnormalities, and heart defects.
- \* The teratogenic potential of lamotrigine and gabapentin remains unclear.
- \* The risk of oral clefts following first trimester benzodiazepine exposure has been estimated at less than 0.6%.
- \* The prevalence of postpartum blues is 50%-75%, while the risk of postpartum depression is 5%-10%, and the risk of postpartum psychosis is 1-2/1000.
- \* Postpartum psychosis typically develops within two weeks of delivery; till proven otherwise it should be considered a manifestation of bipolar disorder.
- \* ECT (with external fetal monitoring and ultrasonography) may be the treatment of choice for the expeditious management of the delusional, depressed, pregnant patient.
- \* There is a high rate of relapse in bipolar women who discontinue lithium during pregnancy.
- \* Treating depression with SSRIs across labor and delivery minimizes the risk for puerperal illness.
- \* Antidepressants of choice during pregnancy include fluoxetine, citalopram, and TCAs.
- \* During pregnancy it is not recommended to switch from one antidepressant to a safer compound, as it is uncertain if the patient will respond to a safer antidepressant in terms of risk/benefit ratio.
- \* Postpartum blues affects 50%-85% of women within the first two weeks after delivery.
- \* Postpartum depression affects 10%-15% of women after delivery; it develops insidiously within the first two to three months.
- \* The manifestations of postpartum depression are similar to those of non-puerperal depression.
- \* Postpartum depression is more common in teen mothers, with inadequate social supports, marital conflict, and negative life events.
- \* Postpartum psychosis develops within the first two weeks delivery in 1 or 2 per 1000 pregnancies.
- \* Postpartum psychosis is a psychiatric emergency; it usually requires treatment with a neuroleptic, a mood stabilizer, or ECT)
- \* A history of bipolar disorder is a prominent risk factor for postpartum psychiatric disturbances.
- \* Lithium reduces the risk of postpartum depression in patients with bipolar disorder or a history of postpartum psychosis.
- \* All psychotropics are secreted into breast milk.
- \* Factors influencing exposure to adverse drug effects in nursing infants include the maternal dosage, the medication dosing schedule, the maternal metabolism of the medication, the maternal volume of distribution, the pH and lipid content of the breast milk, the breastfeeding schedule, and the infant's metabolism of the medication.
- \* Postpartum blues are manifest by mood lability, tearfulness, anxiety, and sleep disturbance. It is a transient disorder that requires no specific treatment.
- \* A history of recurrent MDD or bipolar disorder increases the risk for PPD by 30% and 30-50%, respectively.

## POSTPARTUM PSYCHIATRIC ILLNESS

Ruta Nonacs, M.D., Ph.D.

Dr. Nonacs delivered a comprehensive and practical talk on the prevalence and manifestations of postpartum psychiatric disorders. She also reviewed the treatments for psychiatric illnesses during the post-partum period. Highlights of her presentation include:

- \* The lifetime prevalence for major depression in women is 21.3%; in men it is 12.7%.
- \* Pregnancy is not protective, nor does it reduce the risk for psychiatric illness.
- \* The postpartum period is a time of increased risk for the emergence of psychiatric illness.

## PREMENSTRUAL DYSPHORIC DISORDER

Adele C. Viguera, M.D.

Dr. Viguera presented a comprehensive and data-driven presentation on the nature, course, and treatment of Premenstrual Dysphoric Disorder. She ably reviewed the impact of the changing hormonal environment on mood and behavior.

- \* Criteria for the Premenstrual Dysphoric Disorder (PMDD) involve a one-year duration of mood and somatic symptoms which are present for the majority of



cycles and which are relieved within four days of menses.

- \* PMDD affects 2%-8% of women; it begins at the time of menarche and peaks during a woman's thirties.
- \* Twin and family studies suggest the heritability of PMS and PMDD.
- \* A variety of disorders (e.g., affective, anxiety, psychotic, eating, and personality disorders) as well as substance abuse, migraines, allergies, asthma, and seizures are each exacerbated premenstrually.
- \* PMDD tends to respond more rapidly to use of serotonergic antidepressants than non-serotonergic agents.
- \* Treatments that suppress ovulation (and which lead to improvement in PMDD) include use of GnRH agonists (e.g., Leuprolide, Goserelin, and Nafarelin), Danazol, estrogen, and progesterone.
- \* Many women with PMDD relapse when they stop treatment, as early as one to two cycles.
- \* In spite of the clear efficacy of SSRIs for PMS and PMDD, prescriptions are generally written for oral contraceptives and analgesics by non-psychiatrists.
- \* Calcium supplementation (1200 mg/day) may also be effective for PMDD.
- \* Psychosocial treatments for premenstrual symptoms include psychoeducation, group support, aerobic exercise, dietary changes, and the use of cognitive-behavioral techniques, and stress reduction and relaxation techniques.
- \* Disorders with premenstrual exacerbation include affective and anxiety disorders, psychotic disorders, eating disorders, personality disorders, substance abuse, migraines, allergies, asthma, and seizures.
- \* PMDD may represent an abnormal response to normal fluctuation of steroids.
- \* SSRIs are the first-line option for the treatment of PMDD.
- \* Partial responders on a SSRI might respond by switching to another SSRI, or by use of birth control medications.
- \* PMDD could be treated with SSRIs or by suppressing ovulation with birth control medication.

## EATING DISORDERS

Anne E. Becker, M.D., Ph.D.

Dr. Becker presented a comprehensive review of the diagnostic features, and an approach to the evaluation and management (including the results of recent pharmacological trials) of bulimia and anorexia nervosa.

- \* Anorexia nervosa involves a refusal to maintain minimally normal weight, a fear of gaining weight or gaining weight, and a disturbance in the manner one's weight is experienced.
- \* Bulimia nervosa consists of binge eating, recurrent inappropriate compensatory behaviors to prevent weight gain or purge calories, and a self-evaluation unduly influenced by body shape and weight.
- \* Ninety percent of anorexia and bulimia occur in women.
- \* Anorexia has a slightly earlier age of onset than bulimia.
- \* Sixty percent of cases of bulimia occur in women.
- \* Compensatory behaviors to control weight include induced vomiting, laxative use, abuse of diuretics, compulsive exercise, and restrictive eating or fasting.
- \* Ideal body weight (IBW) can be estimated by the equation:  $IBW = 100\text{lbs} + 5\text{lbs/inch above } 5\text{ ft} + 10\%$  (for females).
- \* Medication management is not the first treatment for eating disorders. However, medications can treat comorbid conditions.
- \* Medical complications of anorexia nervosa include bradycardia, dehydration, hypoglycemia, leukopenia, thrombocytopenia, cardiac arrhythmias, decreased intestinal motility, peripheral neuropathy, amenorrhea, osteopenia, growth retardation, and hair loss.
- \* Medical complications of bulimia nervosa include fluid and electrolyte abnormalities (e.g., low potassium, metabolic alkalosis and acidosis), cardiac arrhythmias, constipation, parotid enlargement, loss of dental enamel, and irregular menses.
- \* Cognitive behavioral therapy (CBT) is effective for bulimia; less is known about its efficacy for anorexia.
- \* No specific medication has been shown effective for anorexia nervosa.
- \* Fluoxetine is the best-studied SSRI for bulimia; it appears safe and effective in controlled trials.



- \* Desipramine and imipramine have each been found superior to placebo for bulimia.
- \* One criteria for inpatient care of the anorectic patient is a body weight < 75% of ideal body weight.
- \* Although bupropion (up to 450 mg/day in divided doses) has been found to be superior to placebo in one study of bulimic patients, it was associated with seizures (prevalence, 5.8%) and is not recommended for bulimic patients.
- \* Sertraline has been found to reduce binge frequency in binge eating disorder.
- \* Fluvoxamine has been found superior to placebo in achieving weight loss in binge-eaters.
- \* Psychotherapy works better than medication in eating disorders and should be tried as a first choice of treatment.
- \* CBT is the best-established psychotherapeutic treatment for bulimia nervosa and binge eating disorder.
- \* Fluoxetine may be effective in weight-recovered anorexics.
- \* Sertraline may be effective in reducing obsessional thoughts about food in anorexia nervosa.
- \* Calcium supplementation is relevant in the treatment of anorexia for osteopenia prevention.
- \* Fluoxetine at a dose of 60 mg a day is the first and only agent to receive FDA approval for treatment of bulimia nervosa; it has been found superior to placebo in treating individuals who had failed either CBT or IPT.
- \* Sertraline and fluvoxamine have been found to reduce binge frequency in binge eating disorder.
- \* Anecdotal case data suggests risperidone and olanzapine may be useful in the treatment for anorexia, as a result of a more flexible thought process rather than as a side effect involving weight gain.

## THE BIOLOGY OF SCHIZOPHRENIA

Donald C. Goff, M.D.

If you ever wondered how the brain gives rise to abnormal thinking and behavior, then you were treated to a remarkable review of the anatomic underpinning and neural circuitry of the brain. Dr. Goff systematically outlined and graphically represented the relationship between neural circuits and their impact on information processing. Presentation of this framework enabled an informed discussion of functional localization. Cytoarchitecture of the cortex, as well as the structure and function of several neuroreceptor systems (dopaminergic, noradrenergic, glutaminergic, GABAergic) were also presented.

- \* Information processing in the brain can be conceptualized as a sequence of three components (i.e., reception, representation, and response).
- \* The relay nuclei (medial geniculate, lateral geniculate, ventral posterior) are the gateway to cortical processing for all incoming sensory information; other nuclei (limbic nuclei, motor nuclei, association nuclei, and intralaminar nuclei) provide modulatory input to cortical and subcortical regions.
- \* The basal ganglia structures (caudate, putamen, and globus pallidus) are primarily involved in the integration of input from cortical motor areas.
- \* Functions, such as memory, language, insight, and consciousness, rely on the proper function of the association cortex.
- \* DLPFC (dorsolateral prefrontal cortex) function is disturbed in schizophrenia.
- \* The hippocampus integrates multimodal sensory information for storage into and retrieval from memory and modulates limbic function via connections to the amygdala and hypothalamus.
- \* Striatal volume is increased in psychosis, most likely due to treatment with antipsychotics.
- \* Hippocampal volume is reduced by about 5% in psychosis.
- \* The most prominent neurotransmitters are the excitatory glutamate and the inhibitory GABA.
- \* Decreased glutamatergic function is thought to be involved in the creation of psychotic symptoms.



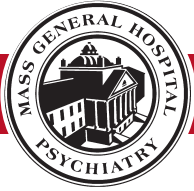
- Disinhibition of GABAergic neurons is impaired in schizophrenia.
- The cortex has pyramidal and nonpyramidal cells, which are arranged in layers; layers 3 and 5 contain pyramidal cells, while layers 2 and 4 are densely packed with nonpyramidal cells.
- Pyramidal cells are glutamatergic, excitatory, output neurons.
- Interneurons are GABAergic and inhibitory.
- Glutamatergic neurons are fast firing.
- The medial dorsal thalamic nucleus is the largest thalamic nucleus and it is abnormal in schizophrenia; it consistently shows a loss neurons.
- Less than half of all the information received from sensory organs makes it to the cortex because of the thalamic filter.
- Cognitive deficits in schizophrenia involve deficits in attention, memory, executive functions, and poor insight; they impair patients in their occupational functioning.
- Hypofrontality in patients with chronic schizophrenia can be seen in functional brain imaging and be correlated with negative symptoms.
- The lateral and third ventricles are enlarged by 10% in schizophrenic patients. Other histopathological changes include a decrease in total gray matter, hippocampal thalamic, and caudate volumes.
- Risk factors for schizophrenia include winter/spring birth, urban birth, perinatal trauma, marijuana use in adolescence, in utero exposure to influenza-rubella, and a family history of schizophrenia.
- Atypical antipsychotics share D2 and 5HT2 antagonism, and a reduced tendency to induce EPS.
- Atypical antipsychotics (clozapine [Clozaril], risperidone [Risperdal], olanzapine [Zyprexa], quetiapine [Seroquel], ziprasidone [Geodon]) are more effective than typical agents (haloperidol [Haldol], fluphenazine [Prolixin], trifluoperazine [Stelazine], thiothixene [Navane], perphenazine [Trilafon], loxapine [Loxitane], molindone [Moban], chlorpromazine [Thorazine], thioridazine [Mellaril], and mesoridazine [Serentil]) for negative symptoms.
- Conventional agents increase the density of post-synaptic D2 receptors (i.e., supersensitivity).
- Conventional agents produce depolarization blockade in A9 (substantia nigra) and A10 (ventral tegmental) dopamine neurons.
- Atypical agents produce dopaminergic blockade in A10 neurons only.
- A9 nigrostriatal neurons are responsible for EPS; A10 mesolimbic neurons are possible associated with psychosis; A10 mesocortical neurons are associated with negative symptoms.
- Hyperprolactinemia is associated with 72% blockade of dopaminergic neurons.
- When 65% of dopaminergic neurons are blocked, efficacy results; when 78% are blocked, EPS and akathisia result.
- Side effects associated with high-potency agents include dystonia, akathisia, and Parkinsonism.
- Side effects associated with low-potency antipsychotics include sedation, hypotension, weight gain, and anticholinergic symptoms.
- Thioridazine is associated with a pigmentary retinopathy at doses > 800 mg/day.
- Neuroleptics impair heat regulation.
- Dystonic reactions induced by antipsychotic agents can be treated with benztropine, diphenhydramine, or diazepam.
- Akathisia may be treated with lowering the neuroleptic dose, or addition of a beta-blocker, an anticholinergic agent, or a benzodiazepine.
- Risk factors for the development of tardive dyskinesia include old age, more than six months of neuroleptic

## THE TREATMENT OF PSYCHOTIC DISORDERS (2 HOURS)

Donald C. Goff, M.D.

Dr. Goff provided the audience with a solid foundation regarding the use of antipsychotic agents; he supported the discussion with details about the basic pharmacology and side-effect profiles of antipsychotics.

- Conventional (typical) antipsychotics or neuroleptics are dopamine D2 blockers, which produce extrapyramidal symptoms (EPS), and elevate prolactin levels.



exposure, a history of Parkinsonian side effects, diabetes, and affective disorders.

- \* Neuroleptic malignant syndrome (NMS) is associated with confusion, muscular rigidity, diaphoresis, fever, mutism, autonomic instability, and elevated CPK.
- \* Clozapine is a weak D2 antagonist, with relatively greater D1 and D4 antagonism; it is strongly anticholinergic, and is an antagonist of alpha-adrenergic, histaminergic, and serotonergic (5HT2) receptors.
- \* Agranulocytosis (<500/mm<sup>3</sup>) occurs in 1.6% of clozapine-treated patients when clozapine is taken for > 52 weeks.
- \* Risperidone is a 5-HT<sub>2</sub> and D<sub>2</sub> antagonist, that also antagonizes D<sub>4</sub>, noradrenergic, and histaminergic receptors.
- \* The pharmacology of olanzapine (Zyprexa) involves a high 5-HT<sub>2</sub>/D<sub>2</sub> ratio and histaminergic and alpha-adrenergic antagonism; its antipsychotic efficacy is comparable to haloperidol.
- \* Side effects of olanzapine include somnolence, constipation, dry mouth, and weight gain.
- \* Quetiapine (Seroquel) has a high D<sub>2</sub>/5-HT<sub>2</sub> ratio. It is an alpha-adrenergic antagonist and it is not anticholinergic.
- \* Ziprasidone is associated with a high 5-HT<sub>2</sub>/D<sub>2</sub> ratio, minimal weight gain, nausea, sedation, and prolongation of the QT interval (possibly greater than other atypicals).
- \* Conventional depot neuroleptics require approximately 4 dosing intervals to achieve steady state; dosing should start with a loading dose or be supplemented by an oral preparation.
- \* Tolerability of an oral preparation should be verified before administration of a depot preparation.
- \* Weight gain associated with antipsychotics is generally as follows: clozapine > olanzapine > quetiapine > haloperidol > molindone.
- \* 20% of olanzapine-treated patients gain >10 kg/year.
- \* Risk factors for QT prolongation include hypothyroidism, substance abuse, cardiac disease, electrolyte disturbance (low potassium or magnesium), use of TCAs, and quinidine.
- \* Conventional antipsychotics tend to be ineffective for cognitive and negative symptoms.

- \* Risperidone may produce EPS at higher doses and elevates prolactin.
- \* Atypicals are very effective in cognitive functioning.
- \* Risperidone delays time to relapse compared with haloperidol.
- \* Tardive dyskinesia typically develops after more than 6 months of neuroleptic exposure.
- \* It is important to use the lowest effective dose of an antipsychotic to prevent tardive dyskinesia.
- \* Occurrence of EPS symptoms is correlated with an 80% receptor blockade, which occurs with 6 mg a day of risperidone and 30 mg a day of olanzapine.
- \* Clozapine and olanzapine produce the greatest weight gain among the atypical neuroleptics.
- \* Quetiapine has a very low incidence of EPS.
- \* There are case reports of insulin resistance associated with atypical antipsychotics that could trigger type II diabetes.

## PSYCHOPHARMACOLOGY OF SLEEP DISORDERS

John J. Winkelman, M.D., Ph.D.

Dr. Winkelman provided a comprehensive overview of sleep architecture and sleep disorders. He covered diagnostic considerations and treatment approaches.

- \* Good sleep practices include using a standardized time for waking, limiting the amount of time in bed, removing the clock from vision, avoiding caffeine before bedtime, and avoiding stressful activities in the evening.
- \* Whenever possible, treat the underlying cause(s) rather than the symptom.
- \* Sleep disorders are often categorized into the:
  - \* DIMS (disorders of initiation and maintenance of sleep)
  - \* DOES (disorders of excessive sleep)
  - \* Disorders of the sleep-wake cycle
  - \* Parasomnias
- \* Chronic insomnia may result from a psychiatric disorder, a medical disorder, the use of licit or illicit substances, a



sleep schedule disorder, restless legs syndrome, or conditioned insomnia.

- \* Restless legs syndrome occurs in 5%-15% of adults; its prevalence increases with age.
- \* In conditioned insomnia there is excessive worry regarding sleep; it begins at the time of stress, but the problem continues after the stress abates.
- \* Treatment of conditioned insomnia involves behavioral treatments (e.g., sleep restriction, relaxation techniques) and the intermittent use of hypnotics to reduce anxiety at bedtime and to reestablish confidence.
- \* REM (rapid eye movement) sleep alternates with NREM (non-REM) sleep at 90-minute intervals. It is associated with a decrease in muscle tone, a high incidence of dream recall if awakened, low voltage random fast activity (with sawtooth waves) on the EEG, and the potential for penile tumescence.
- \* Delta (comprising stages 3 and 4) sleep is the deepest stage of sleep.
- \* Our circadian rhythm typically functions on a 25-hour cycle.
- \* Narcolepsy involves a clinical tetrad, with irresistible sleep attacks (100%), cataplexy (i.e., the loss of muscle tone) often triggered by emotions (90%), sleep paralysis (50%), and hypnagogic hallucinations (30%).
- \* Narcolepsy is a disorder of immediate REM onset.
- \* Sleep apnea is diagnosed by having > 30 apneic episodes during seven hours of REM and NREM sleep.
- \* Obstructive sleep apnea from repetitive upper airway obstruction during sleeps results in oxygen desaturation and/or sleep fragmentation.
- \* Depression is associated with early morning awakening and reduction in REM latency (which normalizes with effective treatment of depression).
- \* Examples of parasomnias include somnambulism (sleepwalking)[which occurs in 15%-30% of children and 1% of adults], night terrors (which occurs in 5% of children), enuresis, and nocturnal bruxism (teeth grinding).
- \* Those afflicted with parasomnias, e.g., sleepwalking, are difficult to arouse during the episode, and are usually amnesic for these behaviors.
- \* Narcolepsy, sleep apnea, or the Klein-Levin syndrome may cause EDS (excessive daytime somnolence).

- \* The principle of sleep medicine is to treat the underlying cause of sleep disruption rather than the symptom.
- \* When treating refractory insomnia it is important to assess for medication side effects, as well as a history of substance abuse, co-morbid psychiatric disorders, and primary sleep disorders.
- \* Some of the medications that produce insomnia include stimulants, steroids, bronchodilators, decongestants, and dopamine antagonists.
- \* The most common cause of restless leg syndrome is idiopathic.
- \* Dopaminergic drugs are generally preferred for the treatment of restless legs syndrome; Pramipexole (at a dose of 0.25 to 1.0 mg q8pm) has also been effective.

## THE TREATMENT OF SUBSTANCE ABUSE (TWO HOURS)

John A. Renner Jr., M.D. and David Gastfriend, M.D.

Drs. Renner and Gastfriend demonstrated their vast clinical experience with alcoholism and other substances and presented a fact-filled presentation on the epidemiology, diagnosis, and neurobiology of substance abuse and substance-related syndromes. They also discussed the medical management of substance abuse at length.

- \* A Blood Alcohol Concentration (BAC) >150 mg% in a person who does not appear very intoxicated, or >300mg% in any awake person is evidence of physical addiction (tolerance) to alcohol.
- \* Delirium tremens (DTs) typically involves a triad of symptoms: confusion, tremor (with hyperactivity), and elevated vital signs; it usually lasts 3-10 days.
- \* Stages of change in the psychiatric management of alcoholism involve precontemplation, contemplation, preparation, action, and maintenance.
- \* Use of antabuse may exacerbate psychosis as it inhibits dopamine beta-hydroxylase and increases CNS dopamine.
- \* Ondansetron, a selective 5HT3 blocker, reduces drinking in early-onset alcoholics.
- \* Use of naltrexone (Revia) reduces the frequency of serious alcohol relapse; it also reduces alcohol craving and euphoria.



- Dysphoria and depression in alcoholics may continue for months or years after detoxification.
- Clinical manifestations of alcohol withdrawal include tremor, paroxysmal sweats, anxiety, agitation, sensory illusions and hallucinations, and disorientation.
- Long-acting benzodiazepines (e.g., chlordiazepoxide and diazepam) are the drugs of choice for most cases of alcohol detoxification.
- Lorazepam may be best for patients withdrawing from alcohol with moderate to severe liver disease because it requires a simpler metabolic degradation pathway.
- Disulfiram (Antabuse) works best for alcohol-abusing patients who are stable, employed, and well supervised.
- When disulfiram-induced hepatitis develops the drug should be stopped promptly.
- Flumazenil (Mazicon) can reverse the effects of benzodiazepine overdose; however, it should not be used in those with benzodiazepine dependence as it may induce benzodiazepine withdrawal seizures.
- Alprazolam is not completely cross-tolerant with other benzodiazepines.
- Acute withdrawal from cocaine requires no specific treatment.
- Bupropion is a first-line approach to nicotine abuse by decreasing nicotine craving via reduction of noradrenergic and dopamine pathways. Its use is contraindicated in those with seizure disorders or bulimia.
- Naloxone (Narcan) can reverse the signs and symptoms of narcotic overdose.
- Clonidine, an alpha-2-adrenergic agonist suppresses firing in the locus coeruleus and reduces symptoms of narcotic withdrawal.
- The prevalence of heroin use is increasing as the purity of the drug has improved and as its cost has decreased.
- Unless exact narcotic doses are known, an initial dose of methadone of 20 mg should not be exceeded when treating presumed narcotic withdrawal syndromes.
- Buprenorphine (a partial opiate agonist) has been found to facilitate opiate detoxification.
- Ecstasy (MDMA, or "X") is associated with an elevation of heart rate and blood pressure, as well as hyperthermia.
- Methamphetamine ("Meth," "Ice," "Speed," "Crystal") may lead to violence, depression, and cardiac arrhythmias.
- Marijuana is the most common illicit drug of abuse.
- After use of phenobarbital, phencyclidine (PCP), and marijuana (delta 9-THC), positive results can be detected on urine toxicology screening tests for more than 3 days.
- Stages of change for substance abuse have been thought to include precontemplation, contemplation, determination, action, maintenance, and relapse.
- Binges of cocaine use may be associated with paranoia, delusions, assaultiveness, or delirium.
- Medical complications associated with cocaine abuse include hypertension, acute myocardial infarction, cardiac arrhythmia, pulmonary edema, stroke, seizures, abruptio placentae, anosmia, nasal septum perforation, HIV infection, and sexual dysfunction.
- Chronic use of cocaine decreases the threshold for CNS neuron firing, which may lead to spontaneous depolarization (manifest by seizures and paranoia), as a consequence of a process known as kindling.
- Naloxone (Narcan) is a pure opiate antagonist with a duration of action of 1-4 hours; its use may precipitate withdrawal in narcotic-dependent individuals.
- Opiate withdrawal may present with diaphoresis, yawning, lacrimation, tremor, rhinorrhea, irritability, dilated pupils, insomnia, tachycardia, hypertension, nausea, vomiting, and abdominal cramps.
- Heroin, methadone, and morphine tend to affect Mu opiate receptors, rather than either delta or kappa receptors.
- Dopamine agonists include bromocriptine, amantadine, pergolide, and mazindol.
- Management of acute PCP intoxication involves verbal reassurance, low environmental stimulation, acidification of the urine (pH < 5.0) to enhance excretion, and when severe, airway protection, IV diazepam, and use of neuroleptics.
- Acute effects of opiates may include analgesia, euphoria, lethargy, smooth muscle inhibition (constipation, urinary hesitancy, miosis), orthostatic hypotension, nausea, and vomiting.



- Naltrexone binds to muopiate receptors and reduces alcohol craving, frequency of relapse and euphoria; dosing is 50 mg q.d. given with meals or antacids to reduce nausea.
- Methadone treatment should begin after documenting withdrawal signs. Unless the exact narcotic dose is known, an initial dose of 20 mg should not be exceeded; it might be repeated in 2 hours if the patient does not respond with the initial dose.
- Typically the methadone maintenance dose is between 60 and 120 mg daily; best results have been seen with doses over 80 mg.
- Phenothiazines are contraindicated in the treatment of PCP as it might lower the seizure threshold.
- Ondansetron, an anti-nausea drug, reduces craving for early-onset alcoholics (type II).
- THC may potentiate the action of both GABA and dopamine by reducing their uptake.
- Use of atypical neuroleptics seems to reduce nicotine smoking in schizophrenics.
- Adjunctive medications in benzodiazepine detoxification include carbamazepine, valproate, gabapentin, sedative antidepressants, beta-blockers, and clonidine.
- Use of cocaine and amphetamines may lead to persistent panic attacks; during abstinence, severe anxiety and depression may develop.
- Hypophoria is a subtle mood disorder characterized by feeling unsatisfied, being uncomfortable among others, and not being happy. It is common to see this in abstinent alcoholics, drug addicts, and adult children of alcoholics.
- Hypophoria might be related to GABA-A system function. Benzodiazepines seem to improve hypophoric mood in abstinent alcoholics.

Carbamazepine, at a daily dose of 600-800 mg, may be more effective than lorazepam in preventing alcohol rebound withdrawal and post treatment drinking in patients with history of multiple withdrawals.

## ADHD ACROSS THE LIFE SPAN

Jefferson B. Prince, M.D.

Dr. Prince presented an exciting, data-driven, and systematic review of the symptoms (including inattention and impulsivity/hyperactivity), the genetics, and the neuroanatomic correlates of Attention Deficit Hyperactivity Disorder (ADHD). He emphasized that ADHD is both prevalent and problematic. Dr. Prince also noted that:

- ADHD is a heterogeneous behavioral disorder with multiple etiologies (neuroanatomical, neurochemical, genetic, and environmental).
- ADHD comprises a deficit in behavioral inhibition.
- Symptoms of inattention include seeming not to listen, avoiding tasks requiring sustained attention, losing things, being easily distractible, and failing to finish tasks.
- Symptoms of ADHD vary in pervasiveness, frequency of occurrence, and degree of impairment.
- Symptoms of impulsivity/hyperactivity include blurting out answers before a question is finished, having difficulty awaiting one's turn, interrupting others, being unable to stay seated, running/climbing inappropriately, having difficulty engaging in leisure activities quietly, and talking excessively.
- Even preschoolers (age 4-6) can be diagnosed as having ADHD.
- The most common type of ADHD is the combined type, which includes inattention-impulsivity/hyperactivity.
- Interestingly, an abnormality in frontal-striatal connections has been observed in ADHD.
- Brain imaging has revealed a smaller right basal ganglia, corpus callosum, and frontal area in those with ADHD.
- Abnormalities in the dopamine transporter gene DAT1 on chromosome 5 and the D4 receptor on the 7 repeat allele on chromosome 11 have been associated with ADHD.
- The neurobiology of ADHD may involve deficits in cholinergic nicotinic receptors.
- There is a highly significant association between maternal smoking during pregnancy and ADHD in the offspring.



- \* Individuals with ADHD receiving medication for ADHD have a lower incidence of substance abuse than those with unmedicated ADHD.
- \* Unmedicated adolescents with ADHD have an increased risk of substance abuse throughout adulthood.
- \* Heritability for ADHD is about 80%.
- \* ADHD occurs equally in boys and girls.
- \* Boys with ADHD tend to have more learning disabilities than girls have disabilities.
- \* ADHD is commonly comorbid with mood, anxiety, and conduct disorders.
- \* Neuropsychological testing has limited diagnostic utility in ADHD.
- \* The times of higher risk of substance use disorder in ADHD are late adolescence and the adult years. Parents of children with ADHD experience higher levels of depression, stress, self-blame, social isolation and marital discord.
- \* Clonidine might be helpful in treating ADHD children with hyperactivity and aggression.
- \* Maternal smoking during pregnancy is a significant risk factor for ADHD in the offspring.
- \* Neuronal networks of attention involve the prefrontal cortex, parietal cortex, cingulate gyrus, limbic structures, basal ganglia, thalamus, and brain stem.
- \* ADHD is five times more likely in children of first-degree relatives with ADHD.
- \* Alcohol exposure, low birth weight, a family history of ADHD, and psychosocial adversity are significant risk factors for ADHD.
- \* Treatment of a child with ADHD may prevent the emergence of substance abuse or dependence between the ages of 15 and 24.

In addition to the daytime lectures summarized above a number of evening seminars were also conducted. They are summarized below.

## MANAGEMENT OF DELIRIUM AND AGITATION IN THE OLDER PATIENT

Menekse Alpay, M.D.

Dr. Alpay delivered a fact-filled discussion of the etiology, manifestations, course, and treatment of delirium; extensive lists of medical causes and diagnostic tests were also provided.

- \* Delirium is one of the most common (10%-40% of hospitalized individuals) and most serious of mental disorders; hospital mortality ranges from 10%-65%.
- \* Delirium involves decreased attention and memory, disorientation, and disturbances in perception, consciousness, and the sleep-wake cycle.
- \* A variety of drugs (e.g., anticholinergics, TCAs, lithium, digitalis, narcotics, corticosteroids), withdrawal states (e.g., secondary to sedative-hypnotics, alcohol), and medical conditions (e.g., hypoglycemia, hypertension, hyponatremia, cardiorespiratory failure, thiamine deficiency, intracranial hemorrhage, head trauma, partial seizures, infections) can induce delirium.
- \* Management of delirium relies on identification and treatment of underlying medical causes and general management of symptoms (with psychotherapeutic, environmental, and pharmacological interventions).
- \* Haloperidol is the high-potency neuroleptic most studied for the management of agitated, delirious states.
- \* Since rare complications associated with use of haloperidol and other neuroleptics are prolongation of the QTc and torsades de pointes (TDP) arrhythmia, levels of potassium and magnesium (which if abnormal may predispose to TDP) should be checked prior to use of haloperidol.
- \* Delirium can be distinguished from dementia by its acute onset, brief duration, fluctuating course, impaired attention, lucid intervals, and abnormal EEG pattern.
- \* There are no reliable symptoms or signs that tell the examining physician what medical illness is causing psychiatric symptoms; only a systematic exam suffices.



- Before a diagnosis can be made, the detailed history of the chief complaint and present illness must be taken.
- The onset (timing) of the present illness is the best clue to causality.
- When considering a differential diagnosis, one should search for vascular, infectious, neoplastic, degenerative, congenital, and traumatic, endocrinologic conditions, as well as states of intoxication, vitamin deficiency, anoxia, and depression.
- The recent APA guidelines mentioned, but did not recommend intravenous treatments for delirium.
- Propofol, a rapidly acting, short duration agent, is often used to manage the agitated, delirious patient in a critical care unit; however, cases of propofol withdrawal may further complicate treatment decisions and patient care.

## MANAGEMENT OF THE DIFFICULT PATIENT WITH SUBSTANCE ABUSE

Lily Awad, M.D.

Dr. Awad presented a practical and fact-filled discussion of the etiology, manifestations, course, and treatment of substance abuse; extensive lists of medical causes and diagnostic tests were also provided.

- Risk factors for schizophrenia and substance abuse include homelessness, violence, verbal threats, multiple medical problems, noncompliance, emergency room visits and hospitalizations, use of high doses of antipsychotics, suicidal ideation, and suicide attempts.
- Patients with schizophrenia report improved attention and concentration when smoking.
- Smokers require twice the amount of traditional antipsychotics than do non-smokers.
- Bipolar patients who are cocaine users tend to be rapid cyclers and to present in mixed states.
- Alcoholics who attempt suicide are more impulsive and less premeditative than those who do not attempt suicide.
- PCP, marijuana, cocaine, as well as other stimulants can cause panic attacks.
- Withdrawal from alcohol, benzodiazepines, sedative-hypnotics, and opiates may be protracted.

## THE RISKS AND CHALLENGES OF TERMINATION OF MEDICATION

Christopher Baethge, M.D.

Dr. Baethge gave evidence of his encyclopedic knowledge of psychopharmacology; he presented data pertaining to antipsychotics and mood-altering treatments. Questions such as, "What is an appropriate role for typical neuroleptics? How do newer neuroleptics compare with older antipsychotics with regard to efficacy? What is an appropriate role for lithium? How do newer and older antidepressants compare with regard to efficacy?" were addressed.

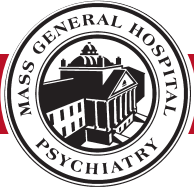
- Long-term use of psychotropics has become increasingly accepted.
- Of mood-stabilizing agents, only lithium has substantial evidence of long-term protective actions against all phases of bipolar disorder.
- Long-term trials of antipsychotics indicate very high rates of relapse or recurrence of psychotic illness within six months of discontinuation of antipsychotics.

## PSYCHOTIC DISORDERS IN CHILDHOOD

Sandra DeJong, M.D.

Dr. DeJong systematically reviewed the manifestations of psychoses in youth, and demonstrated how they differ from psychoses in adults. She also described neurological findings in children with schizophrenia and prepared the audience for the interplay between developmental issues and clinical presentations. Finally, she outlined current treatment approaches for psychotic children.

- Childhood-onset schizophrenia has a male: female ratio of 2-3:1; its onset is insidious and its prevalence is 1 in 5,000.
- In childhood schizophrenia, 80% have auditory hallucinations, 15%-45% have visual hallucinations, and 40%-85% have delusions.
- Negative symptoms seen in childhood schizophrenia include apathy, affective flattening, anhedonia, attentional difficulties, and poverty of speech.
- Children with schizophrenia have a smaller cerebral volume, a smaller thalamic area, and enlarged basal ganglia, and enlarged ventricles, when compared to those without schizophrenia.



- \* Several studies have shown clozapine to be effective in childhood-onset schizophrenia.
- \* Weight gain from olanzapine is greater than that from risperidone or haloperidol.

## GENETICS AND METABOLIC ASSESSMENT OF PSYCHIATRIC PATIENTS

Christine T. Finn, M.D.

Dr. Finn demonstrated the breadth of her knowledge with her articulate overview of the metabolic causes of psychiatric illness. In addition, she provided an elegant overview of the linkage between genetic makeup and expression of disease states.

- \* The goal of behavioral genetics is to understand the relationship between genetic variation and behavioral phenotypes, including mental illnesses.
- \* Identification of the genetic loci that contribute to risk of mental illness and identification of variant forms of the genes found at these loci will provide powerful tools for the investigation of pathophysiology and help determine at what time in brain development cells and circuits are active.
- \* Classical genetic studies have demonstrated a role for heredity in transmission of risk for major psychiatric disorders (e.g., schizophrenia, autism, manic-depressive illness, and early onset major depression).
- \* The metabolic disease work-up includes assessment of food intolerances, neurological symptoms, and developmental delays.
- \* A basic screening work-up for metabolic dysfunction should include investigation of liver function, electrolytes, ammonia, lactate, pyruvate, blood amino acids, urine organic acids, and carnitine.
- \* Wilson's disease involves a mutation in the *ATF7B* gene that leads to a dysfunctional liver, Kaiser-Fleischer rings, and psychiatric symptoms (e.g., cognitive dysfunction, personality change, and emotional lability).
- \* Acute intermittent porphyria involves decreased activity of porphobilinogen deaminase; psychiatric symptoms with this condition are variable.
- \* Homocystinuria presents during childhood; a dislocated lens and thrombotic events often arise.

- \* Lysosomal storage diseases often result in gait disturbance, a decline in school performance, and psychosis.
- \* Mitochondrial disorders involve disorders of fatty acid metabolism and present with a wide variety of symptoms.
- \* Fragile X syndrome is a genetic disorder manifest by large testes, a long face, a large jaw, and a prominent forehead.
- \* Turner syndrome is typically manifest by short stature, neck webbing, gonadal dysgenesis, and hypothyroidism.
- \* Prader-Wili syndrome involves a low IQ, obsessional behavior, temper tantrums, and affective symptoms.

## COMPLIANCE WITH TREATMENT: THE ART AND THE SCIENCE

John B. Herman, M.D.

Dr. Herman led an interactive seminar that highlighted the principles of improvement in a patient's adherence to treatment regimens. He outlined and described several useful strategies.

- \* Adherence to psychotropic regimens by patients is in general not related to income, social class, occupation, or educational background.
- \* Good compliance with psychotropic prescriptions is related to patient satisfaction, continuity of care, and acceptance of the need for treatment.
- \* Poor compliance with medication regimens is related to chronic (symptomatic) disorders, complex treatment regimens, and social dysfunction.
- \* Compliance with medication schedules can be enhanced by linking medication use with daily routines (e.g., meal times, teeth brushing, and bedtime) and building a therapeutic alliance.
- \* Compliance with treatment leads to reduced rates of hospitalization, reduced length of stays, and less recidivism.



## NATURAL MEDICATIONS FOR PSYCHIATRIC DISORDERS

David B. Mischoulon, M.D., Ph.D.

Dr. Mischoulon delivered a fact-filled presentation on natural antidepressants, describing studies of their usage and reviewing their known side effects.

- \* St. John's wort, the world's most popular medication, is effective for mild to moderate depression.
- \* St. John's wort is usually administered as 900-1200 mg/day on a tid basis, although preparations may differ.
- \* Adverse effects of St. John's wort include dry mouth, dizziness, constipation, and phototoxicity; hyperforin (the presumed active ingredient) induces CYP3A4 expression, and interacts with warfarin, cyclosporine, oral contraceptives, theophylline, digoxin, and reduced therapeutic activity.
- \* S-adenosyl methionine (SAME) has a mood elevating effect in depressed people.
- \* SAME depends on levels of B12 and folate in the system.
- \* Recent studies suggest that SAME, at doses up to 1600 mg/day is comparable to the effects of TCAs.
- \* Omega-3 and omega-6, which are essential fatty acids, may have a protective role against depression and bipolar disorder.
- \* Inositol, a precursor of second messenger systems, may reverse desensitization of serotonin receptors.
- \* Small studies suggest inositol may have a role in the treatment of panic disorder and OCD.
- \* Valerian, popular among Hispanics, is a mild hypnotic that may function in a fashion similar to benzodiazepines.
- \* Side effects of valerian include blurred vision, dystonic reactions, and hepatotoxicity.
- \* Kava is believed to have a calming effect.
- \* Kava's suggested doses are 60-300 mg/day; doses should not be taken for more than three months.
- \* Kava is associated with a variety of side effects, including ataxia, hair loss, visual and respiratory problems, and yellowing of the skin.

- \* Many travelers to reset their biological clock when traveling across time zones use melatonin.
- \* Melatonin is an effective hypnotic; it works within one hour of administration regardless of the time of day.
- \* Melatonin is not recommended for pregnant women or for those with compromised immune systems.
- \* Black cohosh, at doses of 40 mg/day, may relieve menopausal symptoms; its side effects include GI upset, headache, dizziness, and weight gain.
- \* Chaste tree berry, at doses of 200-400 mg/day, has been used for relief from premenstrual syndrome; no adverse effects have been reported.

## EMERGENCY PSYCHIATRY

Lawrence Park, M.D.

Dr. Park systematically reviewed the management of the agitated, dangerous, psychotic patient. He presented behavioral, verbal, and pharmacological interventions. In addition, he reviewed a variety of toxic effects of psychotropics (e.g., acute dystonia, akathisia, Parkinsonism, anticholinergic toxicity, and neuroleptic malignant syndrome).

- \* When dealing with an agitated and/or dangerous patient one should move slowly, avoid crowding, and be aware of and control idiosyncratic winking or grinning which could be misinterpreted.
- \* Life-threatening causes of delirium can be recalled by the mnemonic: WWHHHHIMPS (Withdrawal, Wernicke's encephalopathy, Hypoxia, Hypertensive crisis, Hypoglycemia, Hypo/Hyperthermia, Intracranial bleed/mass, Meningitis/encephalitis, Poisoning, Status epilepticus).
- \* General principles of care for the agitated, delirious patient include maximization of patient comfort, correction of metabolic and systemic abnormalities, treatment of drug toxicity/withdrawal, treatment of psychiatric disorders, and use of tranquilizing medications.
- \* Olanzapine is currently available in a wafer form (Zydis) that dissolves instantly in the mouth.
- \* Roughly 90% of cases of acute dystonia secondary to use of neuroleptics occurs within 4-5 days of neuroleptic initiation.



- Risk factors for the development of acute dystonia include being male, being young, having a history of dystonia, and using a high-potency neuroleptic.
- Use of anticholinergic agents (e.g., benzotropine, trihexyphenidyl, or diphenhydramine) prevents acute dystonia.
- Neuroleptic malignant syndrome (NMS) is associated with fever, muscular rigidity, altered consciousness, autonomic instability, and sweating.
- Treatment of NMS involves discontinuation of neuroleptics, supportive treatment (e.g., hydration, nutritional support, external cooling, respiratory and physical therapy), and appropriate pharmacotherapy (e.g., amantadine, bromocriptine, and dantrolene).

- Multi-infarct or vascular dementia tends to show multiple cortical and subcortical infarcts and diffuse atrophy.
- CSF (cerebrospinal fluid) shows up as white on T2 imaging; on T1 images, CSF is shown as black.

## EVALUATION OF SUICIDAL RISK

Theodore A. Stern, M.D.

Dr. Stern provided a well-organized overview of the epidemiology and risk factors for suicide, and outlined key points necessary for the evaluation of suicide potential. He used numerous clinical vignettes (and gallows humor) to highlight the clinical dilemmas associated with the management of suicidal patients. Dr. Stern also reviewed the medico-legal aspects related to suicidal patients.

- Suicide accounts for more than 30,000 deaths each year in the US, resulting in a rate of 12.7/100,000.
- Evaluation of suicidal potential can be complicated by the physicians' emotional reactions (e.g., anger, anxiety) with the patient.
- Take all potentially fatal threats, gestures, and attempts seriously.
- Be empathic; try to establish rapport before honing in on the issue of suicide.
- Ask about suicidal thoughts and intent; determine if there is a detailed plan for suicide and if the means for suicide are available. Also determine if there are plans for the future.
- Review for the presence of risk factors for suicide.
- Protect the patient throughout the evaluation and disposition process.
- Know the laws and procedures in your state for involuntary hospitalization.
- Major depression accounts for 50% of completed suicides.
- Roughly 15% of those with serious, untreated affective illness die by suicide.
- Twenty-five percent of completed suicides are thought to be a result of alcoholism and drug dependence.
- Schizophrenia accounts for 10% of completed suicides; 10% of those with schizophrenia eventually suicide.

## NEUROIMAGING AND PSYCHIATRY

Scott L. Rauch, M.D.

Dr. Rauch provided a comprehensive overview of the currently available neuroimaging techniques (e.g., CT, MRI [with and without contrast, T1 or T2 weighted, and diffusion weighted images [DWI], SPECT [single photon emission computerized tomography], PET [positron emission tomography], fMRI [functional magnetic resonance imaging], MRS [magnetic resonance spectroscopy]).

- CT poorly distinguishes white matter and grey matter, but is good for identifying a fresh bleed.
- MRI is preferred over CT scans of the head when superior soft tissue resolution is desired, when posterior fossa pathology is suspected, or when radiation exposure is contraindicated (e.g., pregnant women or in women of childbearing age).
- Clinical indications for functional neuroimaging in neuropsychiatry include aiding in the differential diagnosis of dementia, and in the evaluation of seizure disorders, movement disorders, stroke, and brain tumors.
- Functional imaging is primarily a research tool; however, PET is more sensitive than SPECT.
- In Alzheimer's Disease, CT and MRI tend to detect diffuse cortical atrophy (greater in the temporal lobes and the hippocampus, with an increase in ventricular volume).
- Bones and calcium are essentially invisible to MRI.



- \* Those who have never married are at highest risk for suicide, followed by those who are widowed, separated, divorced, or married.
- \* Precipitants for suicide include a response to hallucinations or delusions, an escape from pain or suffering, and a response to feeling hopeless, helpless, or trapped.
- \* Be prepared for countertransference reactions to suicidal patients (e.g., anger, hatred, fear, helplessness, indifference, and overinvolvement).