



PSYCHOPHARMACOLOGY NEWSLETTER

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GRAND ROUNDS IN COMMUNITY MENTAL HEALTH

PHARMACOTHERAPY OF PSYCHIATRIC DISORDERS IN PATIENTS WITH COMORBID DRUG AND ALCOHOL ABUSE



This article is adapted from a ground rounds presentation by Steven L. Batki, MD, Clinical Professor, UCSF Dept of Psychiatry; Director, SFGH Division of Substance Abuse and Addiction Medicine

The Significance of Comorbidity

Substance abuse and psychiatric disorders co-exist in a large number of patients, particularly among those seen by public and community mental health systems. Comorbidity is common. For example, the Epidemiologic Catchment Area (ECA) report indicated that 47% of patients with schizophrenia had some form of substance abuse. In fact, schizophrenics had the second highest rate of substance abuse among all psychiatric disorders in the ECA study, with the exception of borderline personality disorder. Among schizophrenics, the prevalence of alcohol abuse was nearly 34% and the prevalence of other drug abuse was nearly 28%. In schizophrenics, studies have shown that the presence of drug and alcohol abuse leads to greater use of psychiatric services, more frequent incarcerations, earlier onset of illness, more positive symptoms, and more disorganization and depression.

Abuse Potential of Psychiatric Medications

The only medications that we need to worry about, with respect to abuse potential, are the benzodiazepines and other CNS depressants, and the psychostimulants, such as methamphetamine and methylphenidate (Ritalin). Generally, all other

psychiatric medications, including antidepressants, antipsychotics, mood stabilizers, non-benzodiazepine anti-anxiety medications, and anti-Parkinsonian medications are not abusable to any significant degree. Occasionally, we do encounter patients who will overuse or misuse anti-Parkinsonian medications or sedating tricyclic anti-depressants, but these are the rare exception rather than the rule (See Table, below).

Abuse Potential of Psychiatric Medications

<u>NO POTENTIAL</u>	<u>LITTLE, IF ANY</u>	<u>ABUSEABLE</u>
antipsychotics	tricyclic anti-depressants	benzodiazepines
lithium	anti-Parkinsonians	other CNS depressants
bupropion	anti-convulsants	methamphetamine
new anti-depressants		methylphenidate

Diagnosis of Substance Use Disorders

Diagnosing substance abuse among patients with psychiatric disorder depends on the same assessments that we use for any other medical or psychiatric problem: history, examination, and laboratory testing. Of these, careful history is the most important. It is helpful to talk to previous caretakers, to look at the medical record, and to ask family members, as patients may seek to mini-

mize or deny their drug and alcohol use. A mental status examination may reveal symptoms that are specific to drug intoxication, for instance hallucinations in unusual modalities (visual or tactile). The physical examination may reveal skin signs of drug use, such as injection marks ("tracks" or old injection scars). Urine drug testing may reveal the use of drugs of abuse, generally for up to 72 hours for most drugs. Breath alcohol testing is useful in individuals who are alcoholic, and blood tests, particularly those that check for liver enzymes such as the transaminases, can show elevations that are associated with alcohol use. Another useful measure is the mean cell volume (MCV) which may be elevated (greater than 100) in the presence of active alcohol use.

Pharmacotherapies for Substance Abuse

What kinds of medical treatments and medications can we use for substance use disorder? In general, the types of medications used for drug abuse involve either 1. replacement or substitution using agonists, 2. the use of antagonists, 3. the use of aversive medications, or 4. medications that seek to correct some underlying psychiatric pathology. Examples of medications that replace drugs are agonists such as methadone for opiates, nicotine for smoking, or benzodiazepines for alcohol withdrawal. An example of antagonism is the use of naltrexone (Revia) for opiate or alco-

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THE USE OF NEW THIRD GENERATION AEDS IN BIPOLAR DISORDER

Renée Williard, RPh, PhD
Peter Forster, MD

Newer third generation anti-epileptic drugs (AEDs) have recently begun to be used by psychiatrists alongside the established second generation AEDs: carbamazepine (Tegretol) and valproate (Depakote). A summary of the use of gabapentin (Neurontin), lamotrigine (Lamactil), and topiramate (Topamax) in bipolar spectrum disorders is presented in the table on page 2.

The effectiveness of gabapentin, lamotrigine, and topiramate in bipolar disorders is currently under study. The literature consists primarily of a limited number of preliminary abstracts, letters to the editor, and small studies of varying quality. All of the reported studies (with the exception of a recent lamotrigine study) have design limitations including open, uncontrolled, or retrospective data; small study sizes; and the confounding use of concomitant medications. Further prospective controlled data are required to clearly establish the effectiveness

of these agents as monotherapy or adjunctive therapy in the various subgroups of patients with bipolar disorder.

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SUMMARY OF THE USE OF THIRD GENERATION AEDS IN BIPOLAR DISORDER

	Gabapentin	Lamotrigine	Topiramate
Pharmacology	Increases GABA levels. Structurally related to gamma-aminobutyric acid (GABA).	Blocks sodium channels and inhibits release of glutamate.	Blocks sodium channels, enhances GABA receptors, and blocks glutamate.
Pharmacokinetics	T1/2 = 5-6 hours	T1/2 = 24 hours Linear pharmacokinetics in doses up to 700 mg.	T1/2 = 20-36 hours Linear pharmacokinetics in doses up to 800 mg.
Route of Elimination	Renal	Hepatic	Primarily renal
Dosage Range	200-3600 mg/day in three divided doses. Generally start with 100mg TID increasing to 200 - 300mg TID.	Initial dose of 12.5-50 mg/day (QD) titrated to a final dose 50-500 mg/day in two divided doses. Titrate by gradually adding 12.5-50mg each week for 8 weeks. Slower titration recommended if patient is on valproate.	Initial dose of 25 mg QD or BID titrated to a final dose between 100 and 200 mg/day, rarely up to 400 mg/day in two divided doses. Titrate by adding 25-50 mg each week for 8 weeks.
Common Side Effects	Somnolence24% Dizziness20% Ataxia17% Fatigue15% Headache15% Tremor15%	Ataxia17-28% Dizziness17-54% Nausea17-25% Headache15-32% Vomiting15-18% Rash10-15%	Somnolence30% Dizziness28% Vision problems28% Psychomotor slowing17% Nervousness16%
Drug Interactions	- Minimal to none (No interaction found with lithium in a single-dose study).	- Carbamazepine may induce metabolism of lamotrigine (reports are inconsistent) and lamotrigine may increase carbamazepine toxicity - Lamotrigine may reduce plasma levels of valproate and valproate may increase lamotrigine concentrations	- Carbamazepine and valproate may lower plasma levels of topiramate by 50% and 15% respectively. - Topiramate may reduce plasma levels of valproate by 10%. - No interactions reported with lithium, gabapentin, or lamotrigine - May lead to decreased effectiveness of some oral contraceptives
Lab Monitoring	None	None	None
Precautions	Dose reduction required in renal impairment	Associated with severe life-threatening rashes*. Lamotrigine should be discontinued at the first sign of rash.	Dose reduction required in renal impairment
Advantages/Indications	- Quite effective for anxiety and pain symptoms - Relatively benign side effect profile - Perhaps most effective for rapid cycling?	- Definitely effective for bipolar depression - Appears to also reduce manic recurrences	- In some patients may cause significant weight loss which can be useful when adding to other agents that cause weight gain - May be effective in rapid-cycling and mixed bipolar states not controlled by carbamazepine or valproate
Disadvantages/Contraindications	- In controlled studies, less effective than lamotrigine in bipolar depression - Dose-dependent bioavailability of 60% for doses of 600 mg or less. Bioavailability decreases substantially for doses > 600 mg.	- Very slow titration needed - Causes rash and rare Stevens Johnson Syndrome*	- Least data on effectiveness; some patients appear to get worse - Some patients are very sensitive to CNS side effects
Cost (per tablet)	100 mg \$0.36 300 mg \$0.91 400 mg \$1.09	5 mg \$1.46 25 mg \$1.54 100 mg \$1.63 150 mg \$1.72 200 mg \$1.80	25 mg \$1.02 100 mg \$2.33 200 mg \$2.72
Cost (per month)	1800 mg/day \$163.80	300 mg/day \$103.20	200 mg/day \$139.80 200 mg/day (split 200 mg tablet) \$81.60
Formulary Status**	AlamedaNF, PAR San FranciscoNF, PAR San MateoF Santa ClaraNF, PAR	AlamedaNF, PAR San FranciscoNF, PAR San MateoNF, PAR Santa ClaraNF, PAR	AlamedaNF, PAR San FranciscoNF, NA San MateoNF, PAR Santa ClaraNF, NA

* The incidence of life-threatening rash with lamotrigine (including Stevens-Johnson syndrome and toxic epidermal necrolysis) is 1/1000 in adult patients and 1/50 in pediatric patients. There are suggestions yet to be proven that the risk of rash may be increased by 1) coadministration of lamotrigine with valproate, 2) exceeding the recommended initial dose of lamotrigine, or 3) exceeding the recommended dose escalation of lamotrigine.

** NF=nonformulary, PAR=prior authorization request, NA=not available, F=formulary

ALAMEDA COUNTY BEHAVIORAL HEALTH CARE

NEW PRIMARY CARE MEDICAL CLINIC OPENING

Richard Singer, M.D.

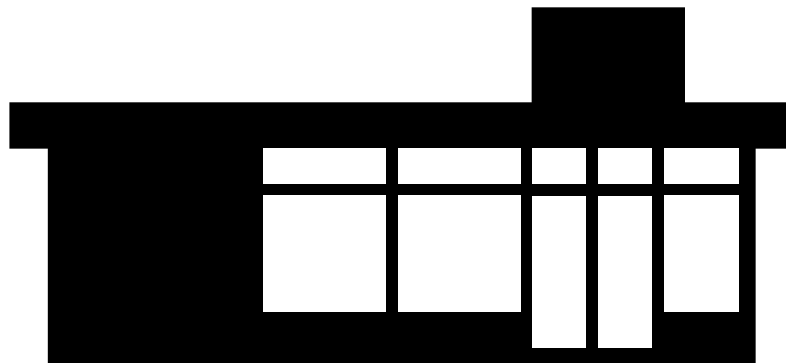
Behavioral Health Care Services, working with Dave Kears, Director of the Health Care Services Agency, is pleased to announce the opening on March 15, 1999 of a new primary care medical clinic designed to accommodate people with mental health problems. Located at 10520 MacArthur Boulevard in Oakland one block from the San Leandro city limits, it is an extension of the already existing medical practice of Uchenna A. Okoronkwo, II, M.D. and Ralph L. Peterson, M.D..

Referrals are being accepted for all adult and child patients, with or without insurance, who may require the medical services of a primary care physician. Working with the clinic staff is a nurse with psychiatric experience, assisting in the provision of both physical health care and primary care-based mental health treatments to patients referred by BHCS mental health programs. Such referrals include the following:

1. Any mental health patient in need of physical health care who does not already have a primary care physician
2. Any mental health patient whose psychiatric symptoms may be caused by a physical medical problem, including organic brain syndrome and mental retardation
3. Adult mental health patients in need of ongoing psychotropic medication maintenance; must be stabilized on psychiatric medication for at least one year with no hospitalizations or Psychiatric Emergency Room visits during that time.
4. Adult patients assessed at ACCESS and determined to have no current need for specialty psychiatric services but whose mild to moderate anxiety or depression could benefit from primary care physician evaluation and treatment.

5. Patients needing physical health care and determined to have behaviors too difficult for most primary care clinics to manage; referral may come from ACCESS as well as any BHCS or primary care clinic
6. Child and adolescent patients who do not already have a primary care physician:
 - a) those with uncomplicated ADHD in need of initial treatment, i.e., without concomitant conditions such as depression, anxiety, aggressiveness
 - b) those with ADHD already being prescribed medication, e.g. from out-of-county; these may either be treated or referred back to ACCESS
 - c) those with ADHD treated by a psychiatrist and stable on medication for at least 6 months; they may or may not continue to have a Level I or III therapist while being medicated by a primary care physician
 - d) those with a mood disorder and stable on medications for at least 9 months

Completion of a standard referral form provided by the Primary Care Medicine Clinic is required for all referrals to the clinic. The



10520 MacArthur Boulevard
Oakland, California

referral process includes:

- a. Call for appointment at (510) 569-7326
- b. Identify that you are from ACCESS or a BHCS program
- c. Complete referral form and either fax to clinic (510) 635-9025, mail it or have it hand carried so it is available when patient is seen by the physician

Timely communication between physicians is an essential element of this primary care/mental health care interface. As with any other primary care physician, telephone consultation with an ACCESS psychiatrist will be made immediately available to the Primary Care Medicine Clinic physician requesting it, as follows:

- a. Call (510) 346-1000 or 1-800-491-9099.
- b. As soon as message starts, push "3" for adult issue, "2" for child issue
- c. When the licensed mental health clinician answers, caller identifies self as a primary care physician wanting direct consultation with a psychiatrist. Caller will be put on a brief hold and the psychiatrist will

Continued on page 4

BHCS FORMULARY ADDITIONS: NEWER ANTI-DEPRESSANTS

As of March 1st, the BHCS Psychiatric Practices Committee added two antidepressants to our medication Formulary. Both venlafaxine (Effexor) and mirtazapine (Remeron) work through blocking several neurotransmitters/receptors in the CNS to provide relief for depression. Venlafaxine blocks the reuptake of the neurotransmitters norepinephrine (NE) and serotonin (5-HT), while mirtazapine stimulates both NE and 5-HT release, through the blockade of the alpha auto-receptor. Both agents have been on the market for over 4 years, and have been prescribed by BHCS psychiatrists in previous responders or medication resistant cases of depression. Some common adverse effects with venlafaxine include dry mouth, insomnia, agitation and sexual dysfunction. Mirtazapine may cause sedation, weight gain and dry mouth. Although both agents are on the MediCal list, with venlafaxine only the extended release form (Effexor XR) is covered. In addition, both agents have a 9-month MediCal prescribing restriction. The average daily cost for the agents is as follows:

Mirtazapine	\$2.20
Venlafaxine	\$3.75

MOSBY'S GENRX ON-LINE

Another benefit of the expanding IS network is the availability of references on-line. Mosby's GenRx is available in an on-line format on our server. This complete resource of all brand and generic medications includes complete medication monographs, an excellent drug/food/lab interaction tool, and search mechanism. Currently, it is available in the BHCS Library, both Access sites, Fremont Family Resource Center (Tri-City) and Eden Community Support. As the network expands, more sites will have this useful resource, as well as others we are exploring.



NEW PRIMARY CARE MEDICAL CLINIC OPENING

Continued from page 3

be immediately contacted, interrupting a session if necessary.

- d. Non-medication, non-medical consultations (e.g. referral to ACCESS information, mental health resources) will be with an ACCESS licensed clinician.

BHCS psychiatrists whose stable patients have been referred to the Primary Care Medicine Clinic will continue to be available for consultation on those patients. In addition, periodic re-assessments by the psychiatrist may be requested by the primary care physician, as clinically indicated.

Finally, unsuccessful attempts to treat patients for their mental health needs in this or any other primary care setting will be referred back to the referring source for further psychiatric assessment and treatment and/or referral to a specialty mental health provider.

Depending on the volume and geographic distribution of referrals, expansion to other areas of the county will be considered as data is collected and analyzed. An oversight committee has been established to address problems as they occur. It meets monthly and any issues concerning services may be routed to either Drs. Okoronkwo and Peterson, or to the Medical Director's Office liaison to the project, Catherine Peterson, R.N. at (510) 567-8108.

For additional information concerning the referral process and to make referrals, the clinic may be contacted at (510) 569-7326.

This is an important first step in the development of primary care services within Alameda County for clients with mental illness and we look forward to expanding these services to those with substance abuse problems as well.

MIA PROGRAM ADDITIONS

It has been over a year since the implementation of the successful BHCS MIA Program. With the co-operation of clients, staff, psychiatrists and network pharmacists, monthly medication costs have been cut by almost 40%, reflected in the continuing policy of open access to newer medications for all BHCS clients. The growing list of medications currently part of this program now includes:

- ◆ Depakote
- ◆ Haldol Decanoate
- ◆ BusPar
- ◆ Serzone
- ◆ Seroquel
- ◆ Prozac
- ◆ Paxil
- ◆ Zyprexa
- ◆ Risperdal
- ◆ Clozaril

GRAND ROUNDS

Continued from page 1

hol dependence. At the present time, we have good pharmacotherapies for opiates and alcohol but relatively poor treatments for stimulants such as cocaine or methamphetamine.

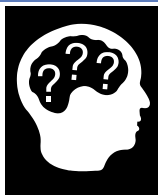
Pharmacotherapy of Psychiatric Disorders

Is it worthwhile to treat psychiatric disorders in patients who are active drug or alcohol users? The answer to this question involves some controversy, but increasing evidence shows that, in particular, treating depression may have beneficial results even among active drug and alcohol users. It certainly lowers depressive symptoms. It is less helpful in actually reducing drug use. Specifically, several studies from the last few years show that using SSRIs or tricyclics can alleviate depressive symptomatology in alcoholics.

Regarding the treatment of other mood disorders, bipolar disorder should certainly be treated even among patients who are active drug and alcohol users. Valproate may be safer than lithium in active drug users. Regarding the treatment of psychosis, again there is clear agreement that pharmacotherapy for psychosis should proceed despite continued drug and alcohol use. Both typical and atypical antipsychotics are probably safe to use, although the newer medications have an advantage in producing less anhedonia. With respect to anxiety disorders, one would seek to avoid the use of potentially abusable medications like the benzodiazepines. Buspirone (Buspar) is useful and safe for Generalized Anxiety Disorders and SSRIs such as sertraline, paroxetine and others, are indicated for the treatment of panic. Venlafaxine is now indicated for panic and generalized anxiety. For sleep disorders, one would proceed in a step-wise fashion, beginning with medications with low abuse potential such as trazodone or hydroxyzine, and use benzodiazepines only with great caution, if at all.

Conclusion

Most psychiatric medications can be safely and effectively used in patients with drug and alcohol use. However, medications are only a small part of the story with respect to the treatment of alcohol and drug use among patients with psychiatric disorders. Our efforts must go into providing psychosocial treatments for these comorbid conditions. The psychosocial treatments should be, by and large, group treatments and ones that focus on several effective psychotherapeutic "technologies". These involve an emphasis on 1) motivational enhancement through counseling, 2) teaching relapse prevention methods to our patients, and 3) encouraging the use of 12-Step and other self-help programs. The most important take-home point for clinicians is to keep a high level of suspicion for comorbid drug and alcohol problems among psychiatric patients and to aggressively provide both psychosocial and pharmacotherapeutic interventions.



DRUG INFORMATION CONSULTATION

Edited by Renee Williard, Ph.D.

Can bupropion (Wellbutrin) be prescribed with ritonavir (Norvir)?

A theoretical interaction has been noted between ritonavir and bupropion that may result in increased plasma levels of bupropion. The interaction between the two is based on the extensive hepatic metabolism of bupropion and the fact that ritonavir inhibits several hepatic enzymes (CYP1A2, CYP2D6, and CYP3A4). The AUC of bupropion (total amount of bupropion present over time in the body) may increase more than 3-fold due to ritonavir's inhibitory activity on liver enzymes. Because bupropion may lower the seizure threshold, co-administration with ritonavir is generally not recommended. SSRIs as a class would be less likely to interact with ritonavir.

Can you provide me with the latest data on the long term incidence of TD with atypical antipsychotics?

Generally, the annual rate of new cases of TD per year for adults was estimated to be 5% with typical antipsychotics (rates for geriatric patients were much higher). Most initial studies with the atypical antipsychotics were of short duration and did not provide data on the long term incidence of TD. Several studies of one year or greater duration have now been completed. We contacted both Lilly and Janssen to obtain post-marketing data for olanzapine and risperidone respectively.

Lilly estimates the incidence of TD with olanzapine to be 1% based on data from 2500 adult patients treated for approximately one year. Glazer (1997) estimated that, excluding patients who developed dyskinesias within the first 6 weeks of treatment, the incidence with olanzapine was 0.6% per year. Janssen estimates the incidence of TD with risperidone to be 0.4%, based on data from patients treated for more than one year (Brecher, 1996, APA Poster). The incidence in geriatric populations is higher, but still considerably less than with typical agents.

PSYCHIATRIC PHARMACY SPECIALIZATION AND BOARD CERTIFICATION


Talia Puzantian, PharmD

The Board of Pharmaceutical Specialties (BPS) was established in 1976 by the American Pharmaceutical Association (APhA). Its purpose is to recognize specialty practice areas, define knowledge and skill standards for recognized specialties, and evaluate the knowledge and skills of individual pharmacist specialties. BPS has recognized five specialty practice areas in pharmacy: Nuclear Pharmacy, Nutrition Support Pharmacy, Pharmacotherapy, Oncology Pharmacy, and Psychiatric Pharmacy.

Most patient care situations are managed effectively by licensed pharmacists not practicing in a specialty area. Other practice settings, such as psychiatric pharmacy may require specialized knowledge and skills, attained only through additional education and experience. Rigorous certification requirements mean that pharmacists in the defined specialty areas can objectively

demonstrate the advanced skills and knowledge necessary to handle difficult and complex patient treatment situations that licensed pharmacy practitioners may not be able to address.

Psychiatric Pharmacy was recognized as a specialty area by the BPS in 1992. The first certification exam was administered in 1996. Since that time, 265 psychiatric pharmacists nationwide have met the requirements for board certification. The specialized psychiatric pharmacist addresses the pharmaceutical care of patients with psychiatric disorders. As a member of a multidisciplinary treatment team, the psychiatric pharmacist specialist is often responsible for optimizing drug treatment and patient care by conducting patient assessments, recommending appropriate treatment plans, monitoring patient response, and recognizing drug-induced problems.

 CONTINUING MEDICAL EDUCATION	
<i>Doug DelPaggio, PharmD</i>	
JUNE 1999	
6/1/99 12:15 - 1:45 p.m.	Managed Care Risk , <i>David Sutton, J.D., LCSW</i> Mills Peninsula Health Services 1783 El Camino Real, Sierra Rooms Burlingame, CA 94010 (650) 573-2530
6/8/99 12:15 - 1:45 p.m.	Gender and Power in Couples Therapy , <i>John Niel, Ph.D.</i> San Mateo County Mental Health Services 225 W. 37th Ave., Multi-Purpose Room, San Mateo, CA (650) 573-2530
6/15/99 12:15 - 1:45 p.m.	Sex and Substance Abuse , <i>Robert Cabaj, M.D.</i> Mills Peninsula Health Services 1783 El Camino Real, Sierra Rooms Burlingame, CA 94010 (650) 573-2530
6/18/99 12 - 2 p.m.	Treatment/medication Compliance Forum, SF CMHS Quality Management 1380 Howard St., 4th Floor Conference Room San Francisco, CA (415) 255-3771
6/22/99 12:15 - 1:45 p.m.	The Narcissistic Pursuit of Perfection , <i>Edward Morehauser, M.D.</i> San Mateo County Mental Health Services 225 W. 37th Ave., Multi-Purpose Room San Mateo, CA (650) 573-2530
6/25/99 11:45 a.m. - 1 p.m.	Case Conference , <i>Presenter: Dr. James Powers, Discussant: Dr. Mark Levy</i> San Francisco General Hospital, 1001 Potrero Ave., Room 7M30 San Francisco, CA (415) 206-4938
SEPTEMBER 1999	
9/16/99 6:30 p.m.	Bipolar Disorder , <i>Mark Frye, M.D.</i> CMH 1380 Howard St., San Francisco, CA (415) 255-3703

**The Bay Area
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