Bay Area

PSYCHOPHARMACOLOGY NEWSLETTER

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SSRI'S: A REVIEW

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With the recent US release of the fifth selective serotonin reuptake inhibitor (SSRI) citalopram (Celexa, Forest Laboratories), it's a good time to review what we know about these agents. This article is largely based on a review of randomized, double-blind, placebo-controlled studies that undertook head to head comparisons of the SSRIs in the treatment of depression (see Table 1). Almost all of the studies referenced were funded by an SSRI manufacturer, and almost all of the studies funded by a manufacturer showed that manufacturer's agent to be equal to or better than the comparison agent, leading one to wonder if there is a publication bias.

There are four studies comparing sertraline (Zoloft) with fluoxetine (Prozac) that meet these criteria. In these four trials, there were no significant differences found on efficacy variables when doses of 50-150 mg/d of sertraline were compared with doses of fluoxetine 20-40 mg/d of fluoxetine.[1,2,3,4] Fluoxetine was associated with more weight loss, dermatological reactions, agitation, anxiety and insomnia. Sertraline was associated with more dyspepsia, somnolence, headache and dizziness.

Many of these studies were large enough to detect clinically significant differences in efficacy or side effects. It is, therefore, difficult to explain the results of one retrospective study of patient self-reported side effects from sertraline and fluoxetine that found almost all side effects occurred more frequently with sertraline than fluoxetine.[5]

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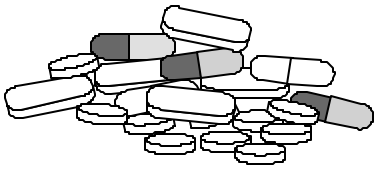

One reviewer suggested that this divergent finding might be due to selection bias; at the time the study was being conducted, sertraline was used most often as a second line agent in patients who had been intolerant of or failed trials with fluoxetine. There are no studies comparing sertraline with paroxetine (Paxil).

There are four studies comparing paroxetine and fluoxetine.[6,7,8,9] One study found a statistically significant early response to paroxetine in a geriatric population (although overall response to either agent in that study was quite low). Three of the four studies showed significantly more weight loss with fluoxetine. One study showed more anxiety with fluoxetine, while another showed more anxiety with paroxetine. One study observed insomnia in nearly twice as many patients in the fluoxetine group as in the paroxetine group.[9]

There is one study comparing fluvoxamine (Luvox) 100-150 mg/d with fluoxetine 20-80 mg/d in patients with moderate depression.[10] This study found the two agents were equally well tolerated and efficacious. Fluvoxamine was associated with less nausea than fluoxetine.

Another study compared fluvoxamine with sertraline in patients with "highly recurrent" unipolar depression followed over 24 months.[11] This study failed to find significant differences in recurrence or side effects. It was, however, a relatively small study.

Finally, another relatively small study compared fluvoxamine 50-150 mg/d with paroxetine 20-50 mg/d; there were no efficacy differences, but paroxetine was associated with more sweating.[12]

The newest agent available in the United States, citalopram (Celexa) has been available in Europe for many years. There is one multi-center, double blind study comparing its efficacy with fluvoxamine in the treatment of depression.[13] Both agents were equally efficacious and citalopram had fewer GI side effects. Another large multicenter double-blind study compared citalopram 20-60 mg/d with sertraline 50-150 mg/d and found no significant differences in efficacy of side effects.[14] Finally, there have been two studies comparing citalopram with fluoxetine.[15,16] Although one study showed more responders in the citalopram group at week 2[15], neither study showed differences in efficacy at endpoint. There were no differences between the two SSRIs in side effects with the exception of more weight loss in fluoxetine-treated patients.

Several studies showed slightly slower response in patients treated with fluoxetine compared to other SSRI's. This may be related to the long half-life and therefore the longer time to steady state for fluoxetine. Fluoxetine also seems to be associated with more agitation and anxiety side effects, but less weight gain and more weight loss.

There are some significant differences among the SSRIs. All of the agents have been associated with a with a serotonin withdrawal syndrome (withdrawal symptoms most commonly include dizziness, parasthesia, tremor, anxiety, nausea and palpitations); however, the rates of withdrawal in patients who abruptly discontinue paroxetine have been consistently higher than with other agents and fluoxetine withdrawal is very rare.[17]

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SSRI'S: A REVIEW

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Paroxetine in one long study, had a slightly higher incidence of sexual dysfunction than the other SSRIs.[18] Another, smaller, study found that sertraline had a larger effect on time to ejaculation than did fluoxetine.[19] A third study suggested that fluvoxamine may have the smallest effect on male sexual function.[20] It seems premature to make too much of these relatively small studies, but there may be differences amongst the SSRI's, and, certainly, some patients who have side effects on one agent may not have these effects on a different agent.

A placebo-adjusted comparison of adverse events reported in the premarketing trials with each of the agents suggests that the most common side effects were nausea (11%), nervousness (10%) and anorexia (7%) with fluoxetine; nausea (26%), drowsiness (17%), constipation (11%) and anorexia (9%) with fluvoxamine; nausea (16%), drowsiness (14%), fatigue (10%), and dizziness (8%) with paroxetine; nausea (14%), diarrhea (8%), tremor (8%), insomnia (8%), drowsiness (7%) and dry mouth (7%) with sertraline; and drowsiness (8%) and nausea (7%) with citalopram.[21]

The newest agent, citalopram, is the most selective SSRI[22], has a relatively benign side effect profile, and has the least potential for drug interactions of all the SSRIs. There has been some controversy about whether it is as safe in overdose as other SSRIs.

SSRI antidepressants are much safer in overdose than tricyclic antidepressants. There have been relatively few fatal overdoses reported involving only SSRIs in the 10 years they have been marketed in the US. In moderate overdoses (up to 30 times the common daily dose), one can expect minor or no symptoms. Larger overdoses may result in drowsiness, tremor, nausea, and vomiting. In very serious overdoses (> 75 times the common daily dose), more serious events including seizures, electrocardiogram changes, and decreased consciousness have been reported with all the SSRI's. In combination with alcohol or other drugs, SSRI overdoses are more serious. There is no apparent difference among the different agents of this class with respect to overdose toxicity.[23]

Based on this review of the published literature, all the SSRIs appear equally efficacious in the treatment of major depressive episodes. There are some differences in side effect profile, although differences in individual patient response may be more important than the data we site. There are also differences in the potential for drug-drug interactions which favor citalopram, and to a lesser extent, sertraline. Fluoxetine is unique in having a very long half-life. This may be useful in reducing the likelihood of serotonin withdrawal, but may also be associated with a slower onset of action. Paroxetine has the highest incidence of withdrawal and may have a slightly higher incidence of sexual side effects.

References in the article can be requested by writing to the Psychopharmacology Newsletter, 2532 Santa Clara Ave., Suite 219, Alameda, CA 94501

TABLE 1: SUMMARY OF SSRIs COMPARATIVE TRIALS

Study	N	SSRIs Compared	Results/Comments
Latimer (1996)[1]	106	sertraline/fluoxetine	no difference in efficacy; more dyspepsia with sertraline; more dermatologic SEs with fluoxetine; significant weight loss with fluoxetine
Sechter (1996)[2]	236	sertraline/fluoxetine	no significant difference in efficacy; both well tolerated; no difference in SEs
Aguglia (1993)[3]	108	sertraline/fluoxetine	no significant difference in efficacy or SEs but more agitation, anxiety, insomnia with fluoxetine and more irritability, headache, somnolence, anorexia with sertraline
Bennie (1995)[4]	285	sertraline/fluoxetine	no significant difference in efficacy; both well tolerated
DeWilde (1993)[6]	100	paroxetine/fluoxetine	no significant difference in efficacy; similar adverse effects
Schone (1993)[7]	106	paroxetine/fluoxetine	geriatric patients; significantly more responders to paroxetine than fluoxetine; both well tolerated
Tignol (1993)[8]	178	paroxetine/fluoxetine	hospitalized patients; no significant differences in efficacy; both well tolerated
Gagiano (1993)[9]	90	paroxetine/fluoxetine	no significant difference in efficacy; well tolerated; insomnia reported twice as often with fluoxetine and decrease in body weight more significant with fluoxetine
Rapaport (1996)[10]	100	fluvoxamine/fluoxetine	no significant differences in efficacy; more nausea with fluoxetine than fluvoxamine
Franchini (1997)[11]	64	fluvoxamine/sertraline	equal efficacy in preventing new recurrences
Kiev (1997)[12]	60	fluvoxamine/paroxetine	equal efficacy; no significant difference in side effects between groups with exception of more sweating with paroxetine
Haffmans (1996)[13]	217	fluvoxamine/citalopram	outpatients; citalopram 20-40 mg/d vs. fluvoxamine 100-200 mg/d; no significant difference in efficacy; relatively low response rates in both groups; significantly more diarrhea and nausea with fluvoxamine than with citalopram
Ekselius (1997)[14]	308	citalopram/sertraline	general practice setting; citalopram 20-60 mg/d vs. sertraline 50-150 mg/d; no difference in efficacy at week 12 though citalopram more effective than sertraline at week 24; no significant difference in SEs; similar reports of sexual SEs
Patris (1996)[15]	357	citalopram/fluoxetine	primary care setting; 20mg vs. 20 mg; significantly more citalopram responders at week 2 but similar response rates by endpoint (8 weeks); weight loss more common with fluoxetine; no difference in other SEs
Bougerol (1997)[16]	296	citalopram/fluoxetine	inpatients and outpatients; 40 mg citalopram vs. 20 mg fluoxetine; similar response rates

San Francisco County
Community Mental Health Services
The San Francisco Mental Health Plan

NEW MENTAL HEALTH DRUG INFORMATION CONSULTATION SERVICE AVAILABLE

Renée Williard, RPh, PhD
Clinical Pharmacist
CMHS Pharmacy Services

The CMHS Drug Information Consultation Service was launched on September 1 in order to respond to telephone questions regarding mental health drug therapy and related problems. The service is available to all San Francisco Mental Health Plan (SFMHP) prescribers and CMHS staff. The goals of the service are:

1) to provide clinical psychopharmacology consultation for SFMHP psychiatrists and CMHS staff, and
2) to develop and support evidence-based drug use policy through comprehensive literature analysis and reviews.

Consultations may relate to:

- dosing and designing drug regimens
- evaluation of drug interactions
- assessment of adverse drug effects
- information on drug stability
- drug use in pregnancy and lactation
- practice guidelines and treatment algorithms
- requests for primary literature related to psychopharmacology

The Drug Information Consultation Service has access to several databases including Medline and PsychInfo for performing literature searches, as well as access to a bibliographic program with over 7000 psychiatric references that can be retrieved within hours.

The Drug Information Consultation Service also serves as a training vehicle for UCSF and UOP pharmacy students. The service is staffed primarily by students with clinical pharmacist supervision. The response you receive will be verbal (via telephone) or, when required, in writing (via fax or mail). The time required for a response depends on the complexity and urgency of the question, and staff resources. Please indicate any special time requirements when your request is made. Our goal is to respond within 1-5 working days. Due to staffing limitations, we are not a STAT service. If you have a pharmacy related question that needs immediate attention, please call the main number for Pharmacy Services (415) 255-3659.

For Your Information...

The Drug Information Consultation Service can be reached by calling (415) 252-3055 with your drug information requests. Requests can be left on voice mail after hours or if no one is available to take your call. The Drug Information Consultation Service is available 9:00 AM to 4:30 PM, Monday through Friday (except holidays).

DRUG INFORMATION QUESTIONS

Efficacy of Gabapentin in Anxiety and Bipolar Spectrum Disorders

The Drug Information Consultation Service received several inquiries in September about the use of gabapentin in anxiety and bipolar spectrum disorders. A summary of the current literature on the efficacy of gabapentin in these disorders follows.

Gabapentin is currently indicated as an adjunctive therapy for the treatment of partial seizures with and without secondary generalization. Initial clinical trails in patients with epilepsy demonstrated some anxiolytic and mood-altering effects. The literature on gabapentin in anxiety and bipolar disorders consists primarily of a small number of preliminary abstracts, letters to the editor, and small studies of varying quality.

Gabapentin is being studied as both monotherapy and adjunctive treatment in bipolar spectrum disorders. Preliminary results from a double-blind trial comparing gabapentin with lamotrigine in monotherapy treatment of bipolar disorder, type I and II indicate a 39% response rate for gabapentin.[1] In two studies that defined diagnostic methods using DSM-IV criteria and utilized rating scales to assess treatment response, one found a 53% (8/15) response (alone or with mood stabilizers) in bipolar depression (type I or type II),[2] and another found a 78% (7/9) response in adjunctive treatment of hypomania, mania, or mixed episodes.[3] An additional study of gabapentin as monotherapy or adjunctive treatment for patients meeting DSM-IV criteria for bipolar disorder or unipolar major depressive disorder found the agent to be effective in 30% (15/50) of patients based on retrospective assessment using the CGI-

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DRUG INFORMATION QUESTION

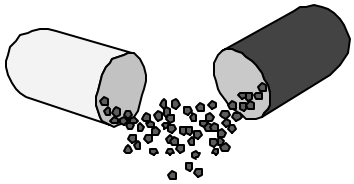
Continued from page 3

I.[4] In a recent case series, gabapentin was added openly as adjunctive therapy in 12 patients with treatment-resistant bipolar spectrum disorders with a non-blindly rated response using the Clinical Global Improvement Scale. Gabapentin was associated with a moderate to marked response in 67% (8/12) of patients, a mild response in 16% (2/12) of patients, and no response in 16% (2/12) of patients.[5] The dosages used in these studies varied widely (100-5600 mg/day).

Data on gabapentin's efficacy in anxiety is also limited. Preclinical data suggest a potential anxiolytic effect of gabapentin.[6] Recently, Chouinard et al.[7] reported reduction in anxiety symptoms and syndromes in a study of 18 psychiatric patients with comorbid anxiety-related disorders. Subjects were treated for at least 12 months and all required concomitant psychiatric medications. Results show that 78% (14/18) of patients had positive clinical responses. Pollack et al. reported on four patients with primary anxiety disorders refractory to standard anxiolytic interventions who experienced marked clinical improvement on gabapentin (200-1200 mg/day).[8]

All of the reported studies of gabapentin in anxiety and bipolar spectrum disorders 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 further clarify the effectiveness of gabapentin as monotherapy or adjunctive therapy in the various subgroups of patients with mood and anxiety disorders.

Gabapentin is a generally safe and well-tolerated anticonvulsant. It is excreted unmetabolized in the urine and has minimal drug interactions. The most common side effects are sedation and ataxia. Dosages range from 200 mg to a maximum of 3600 mg per day and administration does not require plasma monitoring.



Gabapentin is not currently on the CMHS Formulary; therefore, its use in anxiety and bipolar spectrum disorders requires a TAR and is limited to those patients who have failed standard treatments. Gabapentin is currently undergoing evaluation for addition to the CMHS Formulary. Costs per hundred for the 100 mg, 300 mg, and 400 mg capsules are $35.24, $88.12, and $105.73 respectively. Gabapentin (Neurontin®) is marketed by Parke-Davis.

References in this article can be requested by writing to the Psychopharmacology Newsletter, 2532 Santa Clara Ave., Suite 219, Alameda, CA 94501

CMHS PHARMACY BENEFITS MANAGER UPDATE

Chris Woodside,Administrative Analyst CMHS Pharmacy Services

As many of you know, CMHS currently has a contract with St. Mary Pharmacy Management Services who oversees the external pharmacy network for Mental Health. 30,000 mental health prescriptions are dispensed each year from the pharmacy network made up of 30-40 independent and chain pharmacies throughout San Francisco.

CMHS' contract with St. Mary ends December 31 and CMHS is currently in the middle of a request for proposal (RFP) process. We plan to have a new contract in place by January 1, 1999. One of the stipulations of this new contract will be that the pharmacy benefits manager must provide on-line, real time electronic claim adjudication at the point-of-service.

What this means is that the pharmacist will have access to on-line eligibility verification of the prescriber, patient, and payor (whether the prescription will be paid by Medi-Cal, directly by CMHS, through a third party such as PCN, etc.). There will also be a CMHS Formulary check CMHS will, except in unusual circumstances, only pay for prescriptions written by credentialed prescribers writing prescriptions for registered or authorized patients.

Therefore, it is very important that all prescribers who currently utilize the CMHS pharmacy benefits program are either enrolled in CMHS' SFMHP Provider Network or work at a Mental Health city or contract program. If you do not fit one of these categories, please contact Lewis Eng or Chris Woodside at 255-3659 in order for your situation to be researched and to avoid any future disruption of pharmacy services for your patients. Likewise, if you have been using CMHS prescription blanks for non-CMHS enrolled patients, please contact us as soon as possible in order to avoid any future disruption of your patients' pharmacy services.

The PBM will allow us to perform on line adjudication. Instead of using special prescription forms as a way of controlling use of the indigent pharmacy benefit we will be able to verify, in real time, that a prescription was written by a credentialed SF Mental Health Plan physician for a patient who is receiving outpatient treatment and for a covered medication.

Because real time electronic eligibility verification will take place, a customized Mental Health prescription form will no longer be used as a way of controlling access to indigent pharmacy benefits. This new system will also allow CMHS to capture more accurate information about what medications patients are receiving. CMHS hopes to then feed this information back to physicians and to use the information in CMHS' crisis services to ensure that these providers have more accurate patient medication histories.

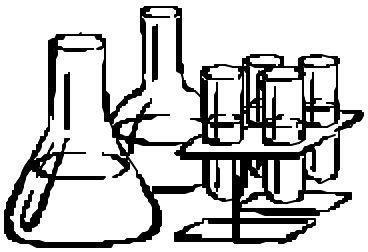
CMHS PHARMACY SERVICES
1380 HOWARD STREET, SAN FRANCISCO, CALIFORNIA 94103
TELEPHONE: (415) 255-3659 FAX: (415) 255-3754

ALAMEDA COUNTY
BEHAVIORAL HEALTH CARE

NEW TESTING SUPPLIES

Richard P. Singer, MD, Medical Director
Douglas DelPaggio, R.Ph, MPA, Director of Pharmacy Services

The Office of the Medical Director now provides several tests to help monitor specific client parameters throughout all BHCS clinics. These include tests for pregnancy, drugs of abuse, and alcohol. Each of these tests is available through the BHCS contract with Drug Testing Resources International, now Worldwide Medical Corporation, in Irvine California.



First Check is a urine test to screen for the presence of cocaine, THC, opiates, amphetamine and PCP. It requires 3 drops of urine, and a 2-5 minutes wait for results. The test is costly at $11.25 per test panel.

First Check hCG rapidly (within 5 minutes) detects the presence of human chorionic gonadotrophin (hCG), a hormone secreted by the developing placenta shortly after fertilization, in the urine. This test costs approximately $1.50 per test.

ALCO Screen O2 is a saliva test for blood alcohol concentrations > 0.02%. By saturating the test pad in saliva and waiting 4 minutes, the presence of a blood level of alcohol is detected by the presence of distinct color line on the test strip. This test costs$2.50 per test strip.

We will continue to evaluate other testing parameters for addition to our contract as they become available.

CALIFORNIA MENTAL HEALTH DIRECTORS ASSOCIATION (CMHDA) COMMITTEE FORMED

As mentioned in the July issue, a Medical Services subcommittee of the System of Care (SOC) Committee of the California Mental Health Directors Association (CMHDA) has been formed to address a variety of medical issues common to all counties. Medical Directors of statewide county Mental Health/Behavioral Health Care Services teleconference monthly and will be attempting to regularly meet several times a year as well.

Goals and Priorities have been developed for 1998-99 and include:

1. Develop a clinical expertise resource base among Medical Services SOC Committee members.
2. Propose and develop further treatment guidelines as requested by the SOC committee.
3. Develop a work group structure for addressing ongoing needs as determined by the SOC committee, e.g., treatment guidelines, LPS clinical issues, pharmacy issues, medical information systems, interfaces with physical health plans.
4. Develop a Medical Services SOC Coordinating Committee with representative membership :
    - superior/small counties
    - bay area counties
    - central counties representative
    - southern counties representative
    - Los Angeles county representative
    - State DMH representative
    - managed care medical services representative
    - children's medical services representative
    - correctional medical services representative
    - older adults medical services representative
    - medical training representative
    - clinical research representative

Establish appropriate working linkages with CMHDA committees and task forces as determined by the SOC Committee.

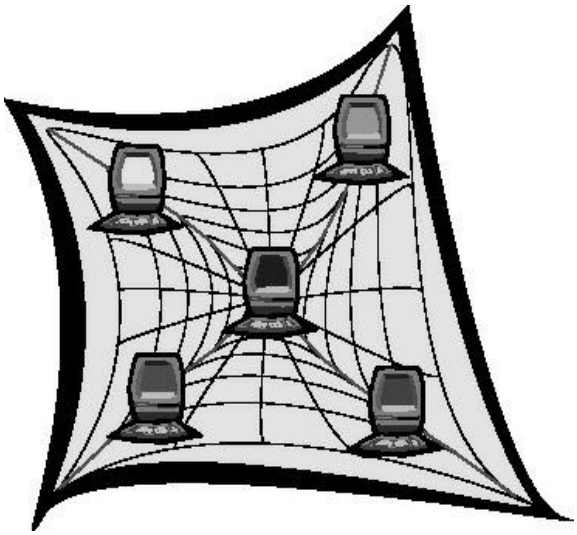
Much work to be done on a wide variety of issues, with more developing all the time. Having the ability to focus on the medical aspects of these issues for an organized contribution to the administrative decision making process, should be of significant benefit to our system of care and the people we serve.

Library Web Sites

The BHCS Medical Library computer has access to the internet. Furthermore, several web sites have been selected as "Favorites" on the computer to help provide clinicians with data resources. The following are brief descriptions of some sites:

www.pie.org

(Policy Information Exchange Online) A subscription service through the Missouri Institute Mental Health (MIMH). Services include free subject searches, free article provision, and access to the library catalog. Also included is access to the Article Database, which is a comprehensive database of mental health policy related articles. Links include associations, foundations, publications, policies and research institutes related to mental health services. Points of Interest is devoted to brief articles which are topical, but not necessarily appropriate for inclusion in the database, for example: "Medicare Expands Crackdown on Waste, Fraud and Abuse in Community Mental Health Centers" Sept 29, 1998. Finally, the Conference Calendar is a comprehensive database of mental health related conferences from around the world.



www.infotrieve.com

MedLine access for information searches. An alternative MedLine search vehicle is available through www.nih.gov

www.medbd.ca.gov

California Medical Board, can check on MD's licensing, file complaints or find a physician.

www.fda.gov

Site is divided into Food, Human Drug, Biologicals, Animal Drug, Cosmetics, Medical Devices/Radiologicals. Under Human Drug, access to the Center for Drug Evaluation and Research, new drug approvals and regulatory guidelines.

www.mcol.com

Managed Care Online, a resource center for professionals involved with managed care. Daily headline news, article library, publications menu, stock resources, links and search facility.

www.samed.com

Scientific American Medicine Online provides monthly CME and highlights of additions to the three-volume text.

www.uhs.bsd.uchicago.edu

Dr. Bob's Psychopharmacology Tips, a well respected site that posts tips from psycho-pharm discussion forums.

www.mhmr.state.tx.us

The Texas Medication Algorithim Project (TMAP) is a landmark study of clinical practice guidelines devoted to mental health services.

www.nimh.nih.gov

National Institute of Mental Health site includes information on the diagnosis and treatment of mental disorders, news and conference listing, grant, contact and research activities.

New Drug Information / Interaction Software

The Office of the Medical Director is currently evaluating a computerized version of **Mosby's** drug reference, **GenRx**.

The software is updated on a quarterly basis, and features many components for medication information. Foremost, an excellent drug interaction assessment program is included. An additional feature includes building individual client profiles with the data provided. Other properties include: complete drug monographs, identifying pictures, three-dimensional chemical structures, disease-specific therapeutic treatment options, and a searchable database for drug information based on drug name, key word, pharmacological or therapeutic class, or indication.

Over the next two weeks, our office will also assess the network aspects of the software, and application to BHCS clinic sites throughout Alameda County.

This program will be available on our library computer by the beginning of October, and at preliminary clinic sites shortly thereafter. Please stop by our Medical Library for a software demonstration over the upcoming month.

San Mateo County
Mental Health Services

PHARMACY BENEFITS MANAGER KICKOFF

It's finally here, can you believe it?!

The long talked about Pharmacy Benefits Manager (PBM) has finally become a reality! We have contracted with MedImpact as the PBM provider, with starting date of October 1, 1998. The Mental Health indigent clients and the Physical Health WELL clients will be eligible on October 1, the Mental Health MediCal clients will join the plan in December. The prescribing procedures and the medication formulary are still similar. The following is a summary of the changes that will take place:

New prescription forms are available and need to be used for the PBM clients, they serve as identifiers of client eligibility. Please check the appropriate plan that the client belongs to (i.e. Mental Health Non-MediCal, WELL Program, etc.), and send or fax the prescription to the pharmacy.

The need for written prescriptions that can be sent or faxed to pharmacies is emphasized in Mental Health Policy No. MH95-07. Phoned-in prescriptions are for emergency or urgent situations only and should always be followed with written version of the prescription.

The Mental Health formulary is similar to the Health Plan of San Mateo formulary, and the WELL formulary is the same as the SMC General Hospital's formulary. If nonformulary medications are needed, please fax the Prior Authorization Request (PAR) to Barbara Liang for Mental Health clients, or Pat Nero for WELL clients. A five-day supply will be dispensed by the pharmacies until the PAR is approved (see PBM Manual, page 19-20).

The formulary is open to revision. Any clinician may request new drugs be added to the formulary, and request will be reviewed by the appropriate committees (see PBM Manual, page 18).

All new clients will be uploaded to the PBM system overnight. The unique prescription form will serve as client eligibility identifier in the interim for the Mental Health clients. The WELL clients must also present their WELL ID card along with the prescription. Client eligibility data can also be individually entered into the PBM system the same day by calling Susie Bass for Mental Health clients at 573-2541, or Rhonda Singh for WELL clients at 573-2486.

An extensive network of local pharmacies have signed on with us (see PBM Manual, page 21), giving clients more choice and improved accessibility.

Questions ???

Questions concerning the WELL Plan, please contact Pat Nero at 573-2366.

Questions concerning the Mental Health Plans, please contact Barbara Liang at 363-4112, ext. 225.

The MedImpact customer service number is 1-800-788-949.

We value your comments and feedback as we implement this new system, please feel free to contact either Barbara Liang at 363-4112, ext. 225 or Bob Cabaj at 573-2403.

PAR VS TAR

Treatment Authorization Request (TAR) is the mechanism by which MediCal clients can obtain non-formulary medications. The Prior Authorization procedure with the PBM is very similar to the Treatment Authorization Request of MediCal. We have adopted the formulary from the Health Plan of San Mateo (HPSM) and their restrictions for now. This formulary is evolving and open to your input. For the time being, the following are the highlights and common examples when a Prior Authorization Request (PAR) will be required:

Benzodiazepines:

- Hypnotics: flurazepam, temazepam and triazolam are restricted to 3 refills every 75 days; in addition, triazolam has a 15 day supply restriction per prescription.
- Antianxiety: only lorazepam and clonazepam are on the formulary, both have restrictions of 3 fills every 75 days, as has been true for the HPSM formulary.
- All other benzodiazepines would require PARs.

Psychostimulants for adults with ADHD need PARs;

Antidepressants:

- Citalopram and clomipramine are not on the formulary, there are no limitations on the length of use.

Antipsychotics:

- Loxitane, molidone and pimozide need PARs;

Anticonvulsants:

- Newer agents such as gabapentin, lamotrigine, tiagabine would need PARs.

PAR forms are available at the clinics. Please fax it to Barbara Liang at 573-2841. Clients will be given a 5-day supply while awaiting the approval of the PAR.

SAN MATEO COUNTY UPDATE

Pediatric Dosing*

Newer Antidepressants and Antipsychotics

DRUG	CATEGORY	AGE*	ORAL DOSE*
Bupropion (*Wellbutrin*)	Antidepressant	6 - 12 y.o.	3 - 6mg/kg divided BID
Fluoxetine (*Prozac*)	Antidepressant	5 - 18 y.o.	5 - 20mg QD
Fluvoxamine (*Luvox*)	Antidepressant	> 8 y.o.	25 - 200mg divided BID
Mirtazapine (*Remeron*)	Antidepressant	no data	no available data
Nefazodone (*Serzone*)	Antidepressant	9 - 15 y.o.	200 - 600mg QD or 3.4mg/kg/day
Paroxetine (*Paxil*)	Antidepressant	< 14 y.o.	10 - 20mg QD
Sertraline (*Zoloft*)	Antidepressant	FDA approved for OCD 6 - 12 y.o > 12 y.o.	 25 - 200mg QD 50 - 200mg QD
Venlafaxine (*Effexor*)	Antidepressant	8 - 12 y.o. 13 - 17 y.o.	12.5mg TID 25mg TID
Olanzapine (*Zyprexa*)	Antipsychotic-Atypical	> 12 y.o.	5 - 20mg QD
Quetiapine (*Seroquel*)	Antipsychotic-Atypical	no data	no available data
Risperidone (*Risperdal*)	Antipsychotic-Atypical	4 - 16 y.o.	0.75mg - 2.5mg QD, max 0.1mg/kg or 6mg QD

* All listed medications, except for fluvoxamine and sertraline, are **not** FDA approved for use in children. The age and dosage ranges listed are derived from clinical trials conducted in children. References are available upon request. Barbara Liang, Pharm.D. 363-4112, ext., 225.

Santa Clara County
Mental Health Services

GABAPENTIN AND LAMOTRIGINE IN THE TREATMENT OF BIPOLAR DISORDER

Marcella Altamirano, Pharm.D. Candidate
University of California, San Francisco

Since its approval by the United States Food and Drug Administration in 1970, lithium has been the only mood-stabilizing agent widely used for bipolar disorder. However, various adverse effects and limitations associated with lithium have prompted efforts to find alternative mood-stabilizing agents. Currently, the most successful alternatives or adjuncts are the antiepileptic agents, carbamazepine (Tegretol) and valproic acid (Depakote). The realization that these antiepileptic drugs have mood-stabilizing properties has increased interest in seeking other antiepileptic drugs possibly containing similar properties.

Gabapentin (Neurontin) and lamotrigine (Lamictal) are new antiepileptic drugs that have been approved by the FDA for partial seizures in adults when used in addition to other antiepileptic drugs. Although controlled studies utilizing these drugs have not been completed on patients with bipolar disorder, several case reports have been conducted. In addition to reviewing case reports regarding gabapentin and lamotrigine, background information such as the pharmacology, mechanism of action, pharmacokinetics, dosing, and adverse effects will be addressed in this paper.

Although the chemical structure of gabapentin is designed similarly to a GABA molecule covalently bound to a lipophilic cyclohexane ring, it does not mimic GABA. Instead, gabapentin appears to increase the promoted release of GABA by an unknown mechanism. The oral bioavailability of gabapentin is approximately 60%. It is rapidly absorbed orally and is not metabolized by the liver in humans. It is eliminated unchanged by the kidney; therefore, patients with renal impairment should be monitored. The half-life is approximately 5 to 9 hours, requiring multiple daily dosing. Additionally, gabapentin does not appear to have any significant drug interactions. This may be attributed to the lack of plasma protein binding and renal excretion.

Gabapentin is usually effective in three divided doses of 900 to 2400 mg/day. However, doses as high as 2400 to 4800 mg/day may be required. Treatment is generally initiated with a low dose of 300 mg at night for three nights. The daily dose is increased in increments of 300 mg every few nights until an appropriate response is achieved. In addition to its short half-life, gabapentin is administered in divided doses because of dose limited absorption across the gut wall. One case trial reported that the initial dose was adjusted in some patients because of gastrointestinal problems such as nausea and diarrhea. Overall, gabapentin is a well-tolerated drug. Somnolence has been reported as the most significant adverse effect. Others include dizziness, ataxia, fatigue, headache, tremors, irritability, and minimal weight gain. Fortunately most of these effects are usually mild to moderate and resolve with time. Similarly to lamotrigine, gabapentin does not require blood level monitoring.

Although clinical trials have not yet been completed, case reports regarding the effectiveness of gabapentin appear promising in patients with bipolar disorder. Gabapentin was successfully administered as a monotherapy to a 40-year old male experiencing manic symptoms, thus demonstrating its antimanic efficacy (Stanton, et al; 1997). In a retrospective study of 73 patients with refractory bipolar disorder, gabapentin demonstrated effectiveness in stabilizing patients with rapid cycling and manic episodes (Ryback, et al; 1997). Eighteen out of 28 patients with refractory bipolar disorder responded positively to gabapentin in another study, while the remaining 10 patients discontinued the drug because of adverse effects or unresponsiveness (Schaffer, et al; 1997). Young, et al. (1997) examined the potential antidepressant effects of gabapentin in patients with refractory bipolar disorder. Eight out of 15 patients responded positively, however, one of the patients who did not respond developed hypomania. Gabapentin also induced hypomania in another patient with epilepsy and mild learning disabilities (Short, et al; 1995).

Lamotrigine is a phenyltriazine derivative that prolongs the inactivation of voltage-dependent sodium channels, thereby blocking the release of excitatory amino acids, glutamate and aspartate. Lamotrigine is completely absorbed orally and metabolized primarily by glucuronidation to an inactive compound in the liver. In addition, it is excreted by the kidney and the half-life is approximately 29 hours. Concomitant administration with enzyme-inducing agents such as phenytoin, carbamazepine, phenobarbital, or primidone increases the clearance of lamotrigine, thereby decreasing the half-life of lamotrigine to 15 hours. However, concurrent administration with valproic acid, an enzyme inhibitor, decreases the clearance of lamotrigine, consequently increasing the half-life to approximately 60 hours. Lamotrigine also affects valproic acid by reducing the concentration of valproic acid by 25%.

The usual maintenance dose for lamotrigine is 100 to 500 mg/day given in two divided doses. Initial treatment doses are generally 50 mg/day for two weeks. The dose is increased to 100 mg/day given in two divided doses for the following two weeks. Thereafter, the dose is increased in increments of 100 mg/day every week until an appropriate response is achieved. The dosing should be reduced in concurrent use with valproic acid. It is important to note that the rate of titration and maintenance dose of lamotrigine varied slightly with each case report, so this dosing guide was obtained from Goodman and Gilman for patients with seizures. Although not significantly different, the rate of titration was slightly faster in the case reports of patients with bipolar disorder.

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Gabapentin and Lamotrigine in the Treatment of Bipolar Disorder

Continued from page 3

Lamotrigine requires a gradual dosage titration, lower starting doses, and caution in concurrent use with valproic acid due to skin rashes. Approximately 10% of the patients administered lamotrigine develop a skin rash, resulting in discontinuation in 2% of the patients. Progression to severe skin rashes such as Stevens-Johnson syndrome has occurred at a rate of 0.1%, possibly requiring hospitalization. Some patients have been successfully rechallenged with lamotrigine after the skin rashes subsided, usually due to slower titration rates. The other adverse effects include dizziness, headache, ataxia, blurred or double vision, nausea, vomiting, and somnolence.

Several case reports suggest that lamotrigine is efficacious in patients with bipolar disorder. The results of a case study involving a 49-year old man in a depressive episode of rapid cycling bipolar disorder demonstrate that lamotrigine has antidepressant effects (Calabrese, et al; 1996). Positive antidepressant effects were also reported by Sporn, et al. (1997), along with mood-stabilizing effects in 8 out of 16 patients with refractory bipolar disorder. However, two patients in this study developed hypomania. In another study, two patients with refractory bipolar depression were successfully treated with lamotrigine, but both developed a slight hypomanic episode (Kotler, et al; 1998). Lastly, two case studies provide evidence that lamotrigine is effective in treating patients with resistant rapid cycling bipolar disorder (Fatemi, et al; 1997. Kusumakar, et al; 1997).

The case studies presented in this article suggest that gabapentin and lamotrigine have potential therapeutic value in the treatment of bipolar disorder. Both drugs appear to be fairly well-tolerated and easily administered. Although these case reports are promising, controlled studies will be necessary to verify the efficacy and safety of gabapentin and lamotrigine in the treatment of bipolar disorder.

ATYPICAL ANTIPSYCHOTIC RETROSPECTIVE SURVEY

This survey was done by the Santa Clara Valley Health and Hospital System, Mental Health Department's Pharmacy. The objective was to determine how many clients were receiving either risperidone or olanzapine as of July 22, 1998. The information was gathered from 7/1/97 through 7/22/98.

Risperidone		Olanzapine	
Started on risperidone	520	Started on olanzapine	692
Remaining on risperidone	334	Remaining on olanzapine	472
Avg. Daily Dose	5.49 mg	Avg. Daily Dose	12.73 mg
Avg. Wholesale Price per day	$7.63	Avg. Wholesale Price per day	$10.96
Avg. Wholesale Price per year	$2,785.00	Avg. Wholesale Price per year	$3,999.66
Receiving risperidone + traditional antipsychotic to control symptoms:		**Receiving olanzapine + traditional antipsychotic to control symptoms:**	
chlorpromazine	4	chlorpromazine	3
perphenazine	5	perphenazine	11
haloperidol	12	haloperidol	16
thiothixene	3	thiothixene	3
fluphenazine	10	fluphenazine	9
thioridazine	1	thioridazine	2
Total	35	trifluoperazine	2
		mesoridazine	1
		Total	47
Receiving risperidone + an atypical antipsychotic to control symptoms:		**Receiving olanzapine + an atypical antipsychotic to control symptoms:**	
olanzapine	3	risperidone	7
clozapine	1	clozapine	2
Total	4	Total	9
Receiving risperidone + an antiparkinson agent to control symptoms:		**Receiving olanzapine + an antiparkinson agent to control symptoms:**	
benztropine	115	benztropine	53
trihexyphenidyl	32	trihexyphenidyl	13
amantadine	4	amantadine	1
Total	151	Total	67
Switched from risperidone to another atypical:		**Switched from olanzapine to another atypical:**	
risperidone to olanzapine	67	olanzapine to risperidone	25
risperidone to olanzapine to quetiapine	3	olanzapine to quetiapine	11
risperidone to olanzapine to risperidone	9	olanzapine clozapine	13
risperidone to quetiapine	3	clozapine to olanzapine	1
risperidone to quetiapine to olanzapine	1	quetiapine to olanzapine	2
risperidone to clozapine	10	clozapine to olanzapine to clozapine	1
risperidone to clozapine to olanzapine	2	olanzapine to risperidone to quetiapine	2

LOCAL CLINICAL TRIALS OF PSYCHOTROPIC AGENTS

Barbara Liang, Pharm.D

Depakote Depression Study
A double-blind, placebo-controlled study for depressed patients with Bipolar I or II disorder. Patients must begin study on no medication. 10 week trial followed by 8 weeks of open treatment. Investigator: Terrence Ketter, MD, (650) 498-4968; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Depakote in Children and Adolescents
A 12 week open label study for children 6-18 with Bipolar I or II disorder with no prior history of treatment with Depakote. Investigator: Kiki Chang, MD, (650) 725-0956; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Estrogen Augmentation in Major Depression
A double-blind, placebo controlled study of fluoxetine with estrogen add-on in women ages18-50 with Unipolar Major Depression. Investigator: Charles DeBattista, MD, (650) 725-4620; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Gabapentin Add-On Bipolar Depression
A 12 week open-label study for patients with Bipolar I or II disorder who are currently taking lithium or Depakote and experiencing depression. Investigator: Terrence Ketter, MD, (650) 498-4968; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Olanzapine vs Depakote in Acute Mania
Double-blind, 3 weeks acute treatment followed by up to 12 months of maintenance treatment. Investigator: Terrence Ketter, MD, (650) 498-4968; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Tiagabine Open Treatment Study
12 week, open treatment trial of tiagabine in bipolar patients with a history of non-response to traditional medications. Investigator: Terrence Ketter, MD,(650) 498-4968; Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine.

Bay Area Research Group ???
Dr. Alan J. Cohen is interested in forming a psychopharmacology clinical research group that would enable local research staff to meet periodically to network and discuss any pertinent issues. If anyone knows of an existing group or is interested in participating in such a group, please call Dr. Cohen at (510) 649-8444.

CROSS CULTURAL PSYCHOPHARMACOLOGY

Barbara Liang, Pharm.D

The rich diversity of the Bay Area requires clinicians to treat an increasing number of psychiatric clients from various ethnic and sociocultural backgrounds. Below we highlight some cross-cultural aspects of psychopharmacology.

General Principles

Culture and ethnicity impact the diagnosis and treatment of mental disorders in many ways: how psychological symptoms are expressed, the different ways of seeking help, and the differences in response to medications and other therapies. Minority groups in general tent to under-utilize mental health resources, and schizophrenia tends to be over-diagnosed in the African and Latino Americans when compared to Caucasians. Pharmacokinetically, differences exist in the absorption, distribution, metabolism and elimination of psychotropics. For instance, plasma protein binding is significantly lower in Asians than in Caucasians and African Americans, leading to higher free drug concentration and potential toxicity. Most psychotropic agents are metabolized via the cytochrome P-450 enzymes, which exhibit genetic polymorphism, resulting in varying degrees of metabolism.

Specific Populations (compared with Caucasians)

	African Americans	Asian Americans	Latino Americans
CYP2D6 (SSRIs, TCAs, some Antipsychotics	33-50% slow metabolizers	33-50% slow metabolizers	33-50% slow metabolizers
CYP3A4 (some benzodiazepines, nefazodone, venlafaxine, CBZ)		lower enzyme activity, due to diet or environmental differences	
Antipsychotics	Over-prescribed, higher doses used, but more sensitive to effects, more likely to develop TD	Need lower doses, greater incidence of EPS observed	Require 30% less dose
Antidepressants	Metabolize TCAs & SSRIs less efficiently; need lower dose and more prone to toxicity	Metabolize TCAs & SSRIs less efficiently; need lower dose and more prone to toxicity	Respond to lower doses, more sensitive to anticholinergic side effects
Lithium	Underprescribed, bipolar misdiagnosed as schizophrenia	Respond to lower therapeutic range and plasma levels (0.3-0.9mEq/1	Bipolar may be misdiagnosed as schizophrenia
Benzodiazepines	Less likely to be prescribed; may be more sensitive to effects	Require smaller doses	One study showed high prevalence of benzodiazepine use

Conclusion

The current literature gives us some broad guidelines about the use of psychotropic agents across the ethnic groups, but we must be cautious in drawing definitive conclusions based upon a limited number of studies, many of which have methodological flaws. As we increase the use of the new atypical antipsychotics and the SSRIs, further studies are needed to delineate the ethnic and cultural aspects of their use.

Ref: Pi EH, Gray GE. A cross-cultural perspective on psychopharmacology. Essent Psychpharmacol. 1998; 2(3):233-260

CONTINUING MEDICAL EDUCATION

Douglas DelPaggio, R.Ph, MPA, Director of Pharmacy Services

NOVEMBER 1998

Family Treatment of Addiction ***Diana Douma, Ph.D.***	**11/10/98** 12:15 - 1:30 PM
Adolescent Substance Abuse, San Mateo County Mental Health Services 225 W. 37th Ave., Multi-Purpose Room , San Mateo, CA (650) 573-2530	
Pharmacoeconomics of Psychiatric Medicine ***Gary Viale, Pharm D., Asst. Clinical Professor UCSF***	**11/10/98** 11:30 -12:30 PM
California Pacific Grand Rounds, 2333 Buchanan St., Conference Center. 1st Floor, San Francisco, CA (415) 922-1920	
Good Reasons for Tough Times: Building Alliances Between Communities and Health Departments	**11/11/98** 3:00 -5:00 PM
101 Grove St., Rm. 300, San Francisco, CA (415) 255-3659	
Long-Term considerations After Switching Antipsychotics ***Peter Weiden, M.D. Columbia University***	**11/19/98** 12:00 -1:00 PM
Alameda County Behavioral Health Care Services 2000 Embarcadero Cove, Oakland, Ca (510) 567-8106	
Atypical Antipsychotic Medications and Outcome in Schizophrenia ***Peter Weiden, M.D. Columbia University***	**11/20/98** 12:00 -1:15 PM
San Francisco General Hospital, 1001 Potrero Ave., Room 7M30, San Francisco, CA (415) 206-4938	
Sex and Substance Abuse ***Bob Cabaj, M.D.***	**11/24/98** 12:15 -1:30 PM
Adolescent Substance Abuse, San Mateo County Mental Health Services 225 W. 37th Ave., Multi-Purpose Room , San Mateo, CA (650) 573-2530	

DECEMBER 1998

Accountability, "Success", and Evaluation	**12/9/98** 3:00 - 5:00 PM
101 Grove Street, Room 300, San Francisco, CA (415) 255-3659	

To have an event listed in January's edition, send it to The Bay Area Psychopharmacology Newsletter, 2532 Santa Clara Ave., Suite 219, Alameda, CA 94501

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