



PINDOLOL AND SELECTIVE SEROTONIN REUPTAKE INHIBITOR

Does the Addition of Pindolol Accelerate or Enhance the Response to Selective Serotonin Reuptake Inhibitor Antidepressants?

By Talia Puzantian, PharmD, BCPP

Adapted from Puzantian T and Kawase K in *Pharmacotherapy* 1999;19(2):205-212.

Even with several antidepressants with differing mechanisms of action, many depressed patients do not respond, respond only partially, or experience a delay in therapeutic response. It has been reported that pindolol, a serotonin 1A (5-HT_{1A}) autoreceptor antagonist, given in combination with selective serotonin reuptake inhibitors (SSRIs) may accelerate and enhance their therapeutic effects. The proposed mechanism of action is that pindolol enhances 5-HT neurotransmis-

sion by blocking 5-HT_{1A} autoreceptors which, when activated, reduce normal firing, 5-HT synthesis, and 5-HT terminal release. What follows is a summary of available published data that addresses this use.

The results of six open trials are summarized in Table 1. Although it is difficult to make definitive conclusions because these studies were not controlled or blinded and involved only small samples, by putting the data together one can see a trend favoring the positive effect of pindolol addition. Of 56 patients taking serotonergic agents (SSRI, buspirone,

nefazodone), 39 (70%) had a decreased latency period of response. Increased efficacy when pindolol was added to a serotonergic regimen was not as much the focus of these trials as was the effect on latency. However, 16 (59%) of 27 patients had increased efficacy with pindolol augmentation. These preliminary results suggested that the drug exerts a significant effect in terms of accelerating response to serotonergic antidepressants such as SSRIs or nefazodone, but not tricyclic antidepressants (TCAs).

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TREATMENT CAN MODIFY RISK FACTORS FOR SUICIDE

Jan Fawcett M.D.

Presented at a Grand Rounds in Community Psychiatry, San Francisco, CA September 23, 1999

Certain clinical risk factors are more effective in assessing acute risk of suicide whereas others are better at assessing chronic risk. Some of these acute risk factors can be modified with treatment if they are recognized. Findings from our research indicates that most of the standard risk factors mentioned in textbooks are probably chronic risk factors. For this reason, recognition of acute risk factors is important in directing timely interventions.

What information is available to us concerning acute risk factors in suicide? The Collaborative Depression Study which compared 13 patients

who committed suicide within one year of assessment with a comparison group yielded several major findings. Among these findings was the presence in suiciding patients of significantly increased comorbid panic attacks (62 percent versus 24 percent), significantly more severe ratings of "psychic anxiety", a significantly higher incidence of "global insomnia" (implying very severe insomnia), and acute moderate severity of alcohol abuse. These findings were recently partially replicated by Hall et al., who studied 100 consecutive cases of suicide attempts severe enough to require hospital admission. On the basis of a standardized interview of these patients, 90 percent reported severe anxiety and 80 percent reported the occurrence of panic attacks shortly prior to their suicide attempt. A recent Swiss study reported on 30 consecutive suicide attempts seen in emer-

gency services where assessment by professional staff was compared with self-report by the patient on a series of psychological dimensions related to the suicide attempt. While professional staff reported their assessment of despair and feeling overwhelmed, the patients reported severe anxiety and a state of emptiness (dissociative anxiety?) leading up to their suicide attempt. A recent study of inpatient suicide records found the presence of severe psychic anxiety, agitation, or both in 79 percent of patients within one week of their suicide.

These findings, taken together, suggest that severe anxiety or agitation symptoms occurring in patients with depression may be important acute risk factors to assess and address therapeutically. While there are no controlled studies to establish that the rapid treatment of severe anxiety symptoms reduces suicide risk, the author's clinical experience suggests that this is the case. We know from clinical experience that if addressed aggressively, anxiety symptoms can be rapidly ameliorated. Controlled studies on this question would be very difficult to conduct, but research in this area is much needed.

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PINDOLOL AND SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS

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STUDY DURATION (WKS)	REGIMEN + PINDOLOL 2.5 MG TID	RAPID ONSET^a	GREATER EFFICACY^a
2	Paroxetine 20mg/d	5/7	NA
2	Various	NA	6/8
4	Paroxetine 20mg/d	7/9	NA
4	Various	NA	10/19
4	Buspirone 30mg/d	9/10	NA
4	Desipramine 150mg/d	0/5	NA
4	Trimipramine 150mg/d	0/5	NA
4	Fluvoxamine 100mg/d	3/10	NA
4	Nefazodone 100mg/d	15/20	NA

^aBased on 50% or greater improvement in HAM-D score (by week 1 or 2 for rapid onset)

Five randomized, double-blind, placebo-controlled studies with a total of 330 patients have been published to date, with mixed results (see Table 2). Taken together, the data suggest that pindolol is effective in some patients in accelerating the response to serotonergic antidepressants. However, whether there are predictors of favorable response remains to be seen, and further study in this regard is certainly needed. For example, in one study, patients who were referred mainly from primary care had more rapid response than those referred by psychiatry. Similarly, another study failed to show a more rapid onset with pindolol, although patients may have had more chronic disease and been more difficult to treat.

STUDY DURATION (WKS)	NO. OF PATIENTS	REGIMEN + PINDOLOL 2.5 MG TID	RAPID ONSET^a	GREATER EFFICACY^a
6	111	Fluoxetine 20mg/d	No	Yes
4	33	Trazodone 100mg/d	NA	Yes
6	80	Paroxetine 20mg/d	Yes/no	NA
6	43	Fluoxetine 20mg/d	No	No
4	63	Paroxetine 20mg/d	Yes	Yes

^aBased on 50% or greater improvement in HAM-D or MADRS (by week 1 or 2 for rapid onset)
^bFour patients received pindolol 5mg bid instead of 2.5mg tid; five patients received placebo bid instead of tid

Evidence from these studies indicate that pindolol accelerates and perhaps enhances therapeutic effects with antidepressant drugs that act by way of serotonin neurons, specifically SSRIs. The difficulty in extrapolating these data into real world practice is due to lack of information on expected response rates, predictors of response, and controlled trials comparing this with other augmentation strategies such as lithium or triiodothyronine. In light of the fact that pindolol is fairly safe and well tolerated, has rapid onset of response, is limited by few contraindications, and is relatively inexpensive, it may be a sensible and valuable addition to the options for treating depression.

SUICIDE: TX CAN MODIFY RISK FACTORS

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Another risk factor for suicide that may be treatable is the trait of impulsivity. Impulsivity is a trait associated with the diagnoses of bipolar disorder, borderline and antisocial personality disorders, and alcohol or substance abuse histories. A number of studies have shown that impulsive, violent, suicidal behavior is associated with measures of low serotonin function in the brain. Recently, a number of studies from Europe have suggested that maintenance treatment with lithium carbonate may significantly reduce the likelihood of suicide in patients with both bipolar and unipolar affective disorders. There is evidence to suggest that lithium carbonate acts by enhancing serotonin function at the second messenger level in the brain. These data suggest the possibility that lithium carbonate maintenance treatment, in addition to its stabilizing effect on mood in bipolar disorder, may specifically address the behavioral dimension associated with suicide in depressed patients. For instance, one study has shown that patients maintained on lithium carbonate had lower suicide rates even if their bipolar disorder was not completely responsive to the treatment. The growing body of clinical data with respect to lithium and the prevention of suicide point to the possibility that this treatment may address a specific behavioral dimension associated with suicide, possibly through its effect on serotonin function. Adding to this possibility is the observation that patients taken off of lithium seem to have increased suicide risk.

We have reviewed data suggesting that severe anxiety/agitation symptoms occurring in depression are acute risk factors for suicide, and that they may be amenable to aggressive anxiolytic treatment. We also reviewed the association of impulsivity with suicide and depression, as well as the data suggesting that lithium carbonate maintenance may reduce suicidal behavior. In this report, I have tried to emphasize the importance of recognizing acute risk factors for suicide and, when possible, trying to reverse factors with treatment. This approach could improve the ability of clinicians to assess suicide risk and prevent suicide in their patients.

A COMPARISON OF ZOLPIDEM (AMBIEN) AND ZALEPLON (SONATA)

By Talia Puzantian, PharmD, BCPP and Glen Stimmel, PharmD Adapted from CNS Special Edition 2000

NON-BENZODIAZEPINE OMEGA-1 RECEPTOR AGONISTS

AGENT	ADULT DOSAGE RANGE	ONSET (MINUTES)	DURATION (HOURS)	T1/2 (HOURS)	COMMENTS
Zolpidem (Ambien), Searle	5-10 mg/d	30-60	2-4	1	
Zaleplon (Sonata), Wyeth Ayerst	5-10 mg/d	30-60	1	1	Very short duration of effect allows dosing during night up to 4 hours before arising

References available on request.

ALAMEDA COUNTY BEHAVIORAL HEALTH CARE

PHARMACY PHACTS: MEDICATION COSTS

Richard Singer, M.D., Medical Director
Douglas DelPaggio, PharmD, M.P.A., Dir. of Pharmacy Services
Mark D. Watanabe, PharmD, PhD, BCPP

With the dawning of the year 2000, our Pharmacy Network marked the beginning of its 4th year of operation. The BHCS Pharmacy System currently covers 21 programs throughout Alameda County, encompasses over 50 pharmacies, and is available for more than 7,500 clients receiving services through BHCS.

The newer antipsychotics (Zyprexa, Risperdal, Seroquel, Clozaril) account for 67% of the prescriptions for antipsychotics written during 1999, a figure higher than the MediCal data for FY 1999 (56%). On a monthly basis, BHCS atypical prescriptions written for the indigent population have risen from 100 (Jan '99) to 180 by the close of 1999 (Chart #1). Financially, these agents account for 85% of the total spending for antipsychotics, the same percentage as reported by the State for MediCal spending. BHCS spent over \$450,000 on these four newer medications last year, although the BHCS MIA Program significantly reduced that spending.

The BHCS MIA Program saved over \$430,000 in 1999 (Chart #2), an 85% increase over 1998 savings! During 1999, the program did encounter some problems with Janssen Pharmaceutica (Risperdal) making their program unavailable to all indigent clients seen through county services, and Smithkline Beecham (Paxil) changing their program to a more difficult process. As a result, direct BHCS costs for both of these agents have sharply risen over the past 6 months.

Overall, the medication budget is similar to spending in both 1997 and 1998 (Chart #3). Through the savings provided through the MIA Program, overall costs have remained static, although more a costly medications are being prescribed. The year 2000 will bring new challenges regarding medication costs, and the newer, more expensive drugs.

CHART #1 TOTAL ATYPICAL PRESCRIPTIONS 1999

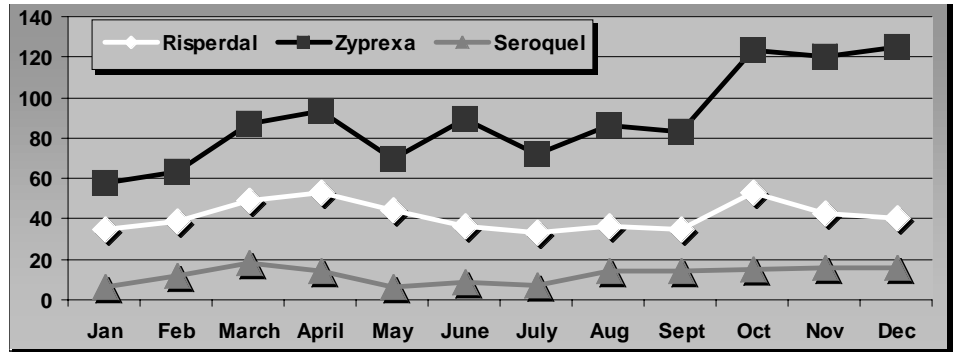


CHART #2 BHCS MIA PROGRAM ANNUAL SAVINGS

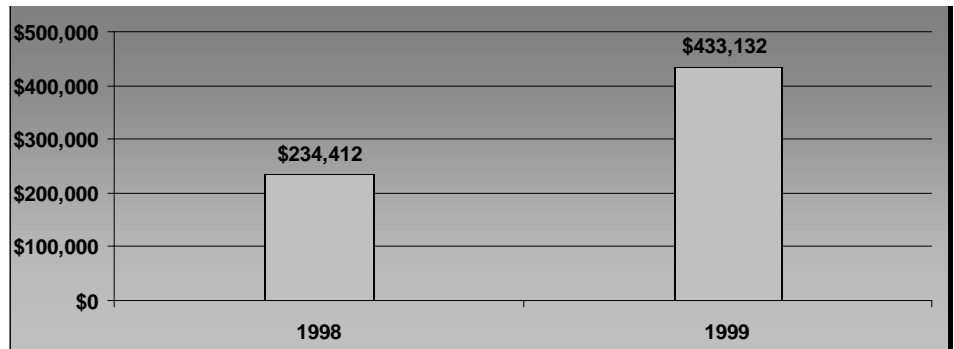
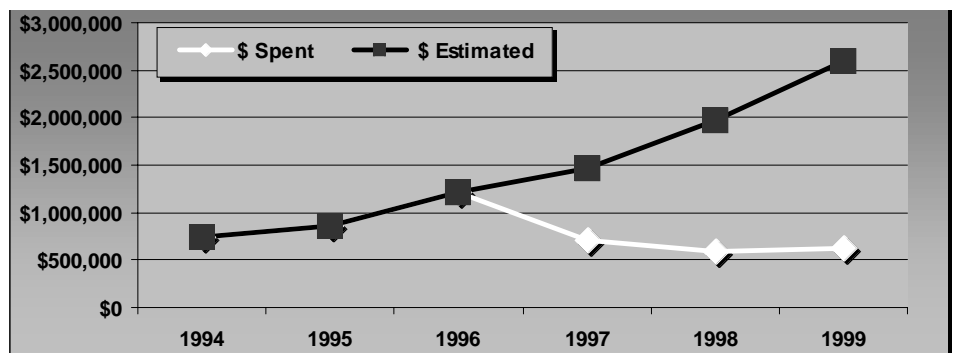


CHART #3 BHCS MEDICATION COSTS 1994 - 1999



THE LPS ACT - FOR BETTER OR WORSE?

There has been considerable activity over the past several months, accompanied by at least as much controversy, since Assemblywoman Helen Thomson (D-Davis) announced her intention to propose changes to the Lanterman-Petris-Short Act. Established in 1969 to outline the conditions under which mentally ill people could be involuntarily hospitalized, proposed changes to the law include expanding the criteria for involuntary commitment, increasing in-hospital detention time, and initiating court-ordered outpatient involuntary treatment.

A series of community forums have been conducted across the State by professional facilitators, with one held in Oakland 11/15/99. They provided the opportunity for people of different views and experiences to express themselves but another result was several common points of interest:

1. Rights Protection - civil rights in any involuntary proceeding, the right to quality care, the right to have basic human needs met, and the right to personal dignity in all legal and treatment situations.
2. Safety - safety of consumers, family members and the general public.
3. Quality of Care - concern that insufficient voluntary, preventive and accessible services leads to unnecessary involuntary treatment or inappropriate treatment (e.g. criminal justice system).

In addition, several major themes emerged across all forums related to desired changes in the current public mental health system rather than the LPS Act itself.

1. Fund community-based services more fully, which may reduce the need for involuntary care. A variety of twenty-three different services were listed.
2. Provide education of law enforcement, judges, the general public and others about mental illness, available treatment interventions and the current LPS legal structure.
3. Enforce the LPS Act more consistently across counties. Better definition of "gravely disabled" was specifically noted.

In addition to the common points of interest and major themes that were more general in nature, different forum participants expressed specific potential amendments to the LPS Act. They included the elimination of involuntary care as well as the expansion of involuntary care to require mentally ill people to receive treatment before meeting current criteria for involuntary hold, or after hospital discharge to ensure compliance with treatment. Others involved expanding the criteria for conservatorships to include "danger to self or others", and the expansion of the Patients' Rights Advocate role and having that Agency no longer report to the Local Mental Health Director.

Another area involved the quantity and content of involuntary holds. It included creation of a 24 hour hold; changing the 14 day hold to 28 days; combining the hearing on an involuntary hold with the hearing on medication; creation of a 28 day hold to follow, if necessary, the 3 day hold; shortening the length of holds while making them easier to renew; shortening or extending the 180 day certification; creating an option to renew the 14 day certification for danger to self.

Still other suggestions related to involuntary holds included either limiting or expanding their criteria, such as:

1. clarifying the definitions of "gravely disabled" and "danger"
2. changing the criteria to take substance abuse into account
3. changing the law so that involuntary holds are made by trained mental health professionals and not law enforcement officers, and/or requiring peer review within 24 hours
4. changing the law to take into account quality (with a clear definition) of life and not just safety.

It is the intention of Assemblywoman Thomson to amend the bill early this year. Whether any of these or other proposals eventually become part of the LPS Act will be debated long and hard and remains to be seen.

CLIENT MEDICATION EDUCATION PROJECT

Alameda County Behavioral Health Care Services is expanding its provision of medication-focused educational sessions for clients served by BHCS clinics. Through participation in these added sessions, to be conducted by BHCS pharmacists, clients will obtain information about the benefits of medications used to treat different brain disorders. The program will focus on how to correctly self-administer medications, evaluate their therapeutic effects, and be able to identify significant side effects associated with different classes of medications.

The working template for the project involves a series of at least three instruction sessions to be held at monthly intervals. The first meeting will be an overview discussion of the types of important questions clients should

ask about their psychiatric medications. Subsequent meetings will review material specific to a particular therapeutic class, i.e., one session devoted to antipsychotics, and another to antidepressants and mood stabilizers. Supplemental medication-specific written information as currently available from BHCS will also be distributed.

Ideally, the sessions will be held in a small group format that allows for useful interactions among clients and staff. Furthermore, ample opportunities would be available to ask questions and discuss information presented. Major teaching points would include names of



medications, types of symptoms treated by the medications, recommended dosage/expected time frames of response, side effect issues, and food or drug interactions (including over-the-counter and street drugs).

The first phase of implementation will take place at two pilot sites, Oakland Community Support Center and Bonita House.

REBOXETINE: AN ANTIDEPRESSANT SHOWCASE FOR NOREPINEPHRINE

Mark D. Watanabe, PharmD, PhD, BCPP

Reboxetine is a novel antidepressant whose mechanism of action involves the selective inhibition of norepinephrine reuptake with minimal effects on other neurotransmitters. Pharmacia & Upjohn, Inc. anticipates releasing this agent sometime in 2000 after receiving final approval from the FDA for the treatment of depression in adults. Its brand name will be Vestra.

A pharmacologically-based discussion of depression has historically focused on the activity of two key neurotransmitters, serotonin and norepinephrine. This is reasonably supportable, given the clinical experience of using known therapeutic agents: Monoamine oxidase inhibitors enhance the effects of both by interfering with their metabolic inactivation; tricyclic antidepressants are known to inhibit the presynaptic reuptake of both from the synaptic cleft; and serotonin reuptake inhibitors (SRIs) are now the most common first-line medications used in the treatment of depression. A growing body of evidence suggests that there may be differential effects of serotonin and norepinephrine as they relate to the pathogenesis of target symptoms associated with the typical depressive episode. By this model, the noradrenergic system modulates drive, energy, learning and memory, and the serotonergic system modulates mood; both may functionally overlap in modulating sleep disturbances and anxiety.

The introduction of venlafaxine, a dually-active agent which selectively inhibits the reuptake of serotonin and norepinephrine, possibly rekindled an awareness that remediation of dysfunctional noradrenergic as well as serotonergic systems may be necessary to provide additional benefit to patients who may not fully respond (or are intolerant) to the selective SRIs. Reboxetine, in a sense, represents a further swing of the pendulum toward noradrenergic mechanisms because of its potent and selective *in vitro* inhibition of CNS neuronal reuptake of norepinephrine (with a 64- to 133-fold weaker potency on serotonin reuptake and negligible effects on dopamine reuptake). Reboxetine only has a slight affinity for serotonergic 5HT_{2C}, histamine H₁, and muscarinic cholinergic receptors, and no significant affinity for adrenergic (α_1 , α_2), dopaminergic (D₂, D₃, D₄), or serotonergic 5HT_{1A} or 5HT_{2A} receptors.

Activities at these receptors are thought to be associated with the various anticholinergic, sedative, and cardiovascular side effects often seen with psychotropic medications. In addition, reboxetine also appears to exhibit only weak inhibitory effects on monoamine oxidase B and no effects at all on monoamine oxidase A.^{1,2}

The molecular structure of reboxetine allows it to exist in several three-dimensional orientations known as enantiomers, two of which will be present as a mixture in the commercial formulation (one of which is more pharmacologically potent than the other). In human volunteers, the elimination half-life for both enantiomers were found to be similar at about 12-16 hours, with the time to reach peak plasma concentrations approximating 2 hours. It is extensively bound to plasma proteins, Reboxetine particularly α_1 -acid glycoprotein, and ingestion of food does not seem to have a significant effect on overall bioavailability. Reboxetine is also extensively metabolized by the liver. Although hepatic impairment may therefore decrease its metabolic clearance, small studies in patients with alcoholic liver disease have not demonstrated any additional adverse events; therefore, recommendations for across-the-board dosage reductions in this population remain unclear. However, since reboxetine and its metabolites are excreted primarily in the urine, the effect of renal impairment on reboxetine pharmacokinetics are potentially more profound and significant, suggesting that a dose reduction is definitely warranted in patients with renal insufficiency. Likewise, because of age-dependent decreases in kidney function, dosages should be reduced in the elderly.

Reboxetine itself is metabolized by the cytochrome P450 3A4 isozyme (CYP3A4), and does not cause appreciable inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.²

In comparative clinical trials, reboxetine 4-8 mg/day (given on a b.i.d. regimen) was found to be superior to placebo and as effective as 100-200 mg/day desipramine after a four-week trial in hospitalized depressed patients³ and 150 mg/day imipramine after a six-week multicenter trial involving both inpatients and outpatients being treated for a major depressive episode.⁴ The onset of therapeutic

effect as determined by statistically significant differences from placebo was also found to occur earlier with reboxetine compared to desipramine (14 days vs. 21 days).³ In a study which compared 8-10 mg/day reboxetine to 20-40 mg/day fluoxetine in another multicenter protocol which enrolled depressed participants from inpatient and outpatient/day hospital settings over 8 weeks, both antidepressants were similarly effective in reducing the severity of depression (each with greater efficacy over placebo).⁵

Because major depressive disorder is gaining recognition as a chronic illness, it is also important to identify antidepressants which demonstrate efficacy in preventing relapse and recurrence of illness in addition to their success in treating an acute episode. To this end, a placebo-controlled study was designed to assess the long-term efficacy and tolerability of reboxetine 8 mg/day in patients with a diagnosis of major depressive disorder, recurrent, and who had responded to an initial 6 weeks of treatment.⁶ Subjects were followed for a subsequent 46 weeks in a double-blind phase and tracked for rates of relapse, which was defined as $\geq 50\%$ in the total score on the Hamilton Rating Scale for Depression. The reboxetine group was found to have a markedly lower relapse rate than placebo (22% vs. 56%).

In all studies, reboxetine was reasonably well tolerated. The most commonly reported side effects in the published trials included insomnia (6-13%), increased sweating (8-18%), urinary hesitancy or retention (8-11%), constipation (17-28%), and dry mouth (22-45%). There were no notable or clinically significant alterations detected in vital signs, laboratory parameters, or electrocardiogram monitoring.^{3,5,6}

As with any newly introduced medication, additional clinical experience and research is needed to further define the place of reboxetine in the antidepressant pharmacopeia. Its unique mechanism of action among currently marketed agents may certainly pique the interest of clinicians seeking new alternatives with demonstrated therapeutic efficacy.

References available on request.



CONTINUING

MEDICAL EDUCATION

Doug DelPaggio, PharmD MPA

MILLS PENINSULA HEALTH SERVICES
1783 El Camino Real Sierra Rooms
Burlingame, CA 94010 (650) 696-5313

Discussion of Life & Death Options with Terminally Ill Clients, *Peter Goldblum, Ph.D.*
March 7, 2000 12:15 - 1:45 pm

Update on the Diagnosis in the Management of Depression, *Mark Rappaport, M.D.*
March 21, 2000 12:15 - 1:45 pm

Psychotherapy with Cancer Patients, *Norman Postone, M.D.*
April 4, 2000 12:15 - 1:45 pm

The Treatment of Social Phobia, *Edward Morhauser, M.D.*
April 18, 2000 12:15 - 1:45 pm

Success of Failure: The Complexity of Assessment *Alan Skolnikoff, M.D.*
May 2, 2000 12:15 - 1:45 pm

Travel Through Crime, *William DeLeon*
May 9, 2000 12:15 - 1:30 pm

Improving the Management of Anxiety Disorders, *Carolyn N. Gracie, M.D.*
May 16, 2000 12:15 - 1:45 pm

SAN FRANCISCO GENERAL HOSPITAL
1001 Potrero Ave., Room 7M30
San Francisco, CA (415) 206-4938

Management Options for Drug-Induced Orgasmic Dysfunction, *Glen Stimmel, Pharm.D.*
March 10, 2000 12 noon - 1 pm

Mood and Anxiety Disorders in HIV Positive Patients, *Dan Karasic, M.D.*
March 24, 2000 12 noon - 1 pm

Use of Atypical Antipsychotics in Bipolar Disorder, *Terrence Ketter, M.D.*
April 21, 2000 12 noon - 1 pm

Psychosis and Antipsychotics in Late Life, *Dilip Jeste, M.D.*
April 28, 2000 12 noon - 1 pm

The Management of Movement Disorders Associated with Antipsychotic Therapy, *Richard Trosch, M.D.*
May 12, 2000 12 noon - 1 pm

Clinical Culture vs. Evidence in the Management of the Agitated, Psychotic Patient, *Michael Allen, M.D.*
June 9, 2000 12 noon - 1 pm

SAN MATEO COUNTY MENTAL HEALTH SRV.
225 W. 37th Ave., Multi-Purpose Room
San Mateo, CA (650) 573-2530

Hypnosis, *Thomas Nagy, M.D.*
March 14, 2000 12:15 - 1:30 pm

Self Mutilation & Borderline Organization, *Jeffrey S. Kline, Ph.D.*
March 28, 2000 12:15 - 1:30 pm

Acupuncture, *Jeff Gould, M.D.*
April 11, 2000 12:15 - 1:30 pm

Brain Imaging in Neuropsychiatric Disorders, *Allen L. Reiss, M.D.*
April 25, 2000 12:15 - 1:45 pm

Dual Diagnosis Summit, *Rick Ries, M.D.*
March 16, 2000 8 am - 4 pm
Health Education Center
Bechtel Auditorium 400 Hawthorne Ave.
Oakland, CA 94609 (510) 567-8106

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