Rethinking Psychiatric Care:

If We Follow the Scientific Evidence, What Must We Do To Better Promote Longterm Recovery?

The Common Wisdom

The introduction of Thorazine into asylum medicine in 1955 "initiated a revolution in psychiatry, comparable to the introduction of penicillin in general medicine."

--Edward Shorter, A History of Psychiatry

The Disabled Mentally III in the United States, 1955-2007

(under government care)

Per 100,000 population



Source: Silverman, C. The Epidemiology of Depression (1968): 139. U.S. Social Security Administration Reports, 1987-2007.

U.S. Disability in the Prozac Era

Millions of adults, 18 to 66 years old



Increased Treatment and Disability In U.S., 1990 to 2003

| | 1990 | 2003 |
|---|---------------|---------------|
| Number treated for psychiatric disorders | 11.16 million | 21.77 million |
| Number on government disability due to mental illness | I.47 million | 3.25 million |

Source: Surveys on prevalence of psychiatric disorders in 1990 and 2003, and percentage of those with disorders who were treated; SSI and SSDI disability data for 1990 to 2003.

The Chemical Imbalance Theory of Mental Disorders

- Arose from understanding of how drugs act on brain (1960s-1970s)
- Investigations of dopamine theory of schizophrenia and serotonin theory of depression started in 1970s

Findings re the Chemical Imbalance Theory of Mental Disorders

A. Serotonin Theory of Depression

• "Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression." --NIMH, 1984.

• "There is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no real monamine deficit."--Essential Psychopharmacology, 2000

• "After more than a decade of PET studies, monamine depletion studies, and genetic association analyses examining polymorphisms in monaminergic genes, there is little evidence to implicate true deficits in serotonergic, noradrenergic, or dopaminergic neurotransmission in the pathophysiology of depression. This is not surprising, as ther is no a priori reason that the mechanism of action of a treatment is the opposite of disease pathphysiology." Eric Nestler, "Linking Molecules to Mood," 2010.

B. Dopamine Theory of Schizophrenia

• "There is no compelling evidence that a lesion in the dopamine system is a primary cause of schizophrenia." *Molecular Psychiatry*, 2002

C. Chemical Imbalance Theory of Mental Disorders (in general)

• "We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them." Kenneth Kendler, *Psychological Medicine*, 2005.

A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

• Psychiatric medications "create perturbations in neurotransmitter functions."

• In response, the brain goes through a series of compensatory adaptations in order "to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu."

• The "chronic administration" of the drugs then cause "substantial and longlasting alterations in neural function."

• After a few weeks, the person's brain is now functioning in a manner that is "qualitatively as well as quantitatively different from the normal state."

Source: Hyman, S. "Initiation and adaptation: A paradigm for understanding psychotropic drug action." Am J Psychiatry 153 (1996):151-61.

The Evidence for Psychiatric Drugs

Short-term Use

The medications reduce target symptoms of a disorder better than placebo in six-week trials.

Long-term Use

In relapse studies, those withdrawn from the medications relapse at a higher rate than those maintained on the medications. See antipsychotics in particular.

Clinical Perceptions

The physician sees that the medications often work upon initial use, and sees that patients often relapse when they go off the medications.

What's Missing From the Evidence Base?

A. It does not provide evidence that medications improve the longterm course of major mental disorders, particularly in regard to functional outcomes.

B. The relapse studies reflect risks associated with drug-withdrawal effects, rather than just the return of the natural course of the disorder. This heightened risk of relapse is due to the fact that the brain has been changed by exposure to the drug.

C. The medical profession no longer has an understanding of the "natural course" of major mental disorders, such as depression, bipolar disorder, and psychotic disorders, and thus its clinical perceptions about the efficacy of the drugs isn't informed by that long-term perspective.

Assessing Long-Term Outcomes

"If we wish to base psychiatry on evidencebased medicine, we run a genuine risk in taking a close look at what has long been considered fact."

--Emmanuel Stip, European Psychiatry (2002)

Schizophrenia Outcomes, 1945-1955

• At end of three years following hospitalization, 73 percent of first-episode patients admitted to Warren State Hospital from 1946 to 1950 were living in the community.

• At the end of six years following hospitalization, 70% of 216 first-episode patients admitted to Delaware State Hospital from 1948 to 1950 were living in the community.

• In studies of schizophrenia patients in England, where the disorder was more narrowly defined, after five years 33% enjoyed a complete recovery, and another 20 percent a social recovery, which meant they could support themselves and live independently.

Source: J Cole, *Psychopharmacology* (1959): 142, 386-7. R. Warner, Recovery from Schizophrenia (1985): 74.

The First Hint of a Paradox

NIMH's First Followup Study (1967):

At the end of one year, patients who were treated with placebo upon initial hospitalization "were less likely to be rehospitalized than those who received any of the three active phenothiazines."

Source: Schooler, C. "One year after discharge." Am J of Psychiatry 123 (1967):986-95.

Bockoven's Retrospective Comparison of Outcomes in Pre-Drug and Drug Era

Samuel Bockoven's Understanding of the Natural Course of Mental Disorders:

"The majority of mental illnesses, especially the most severe, are largely self-limiting in nature if the patient is not subjected to a demeaning experience or loss of rights and liberties."

Results of his retrospective study of first-episode patients:

1947 cohort: 45% didn't relapse within five years of discharge, and 76% were successfully living in the community at the end of that period.

1967 cohort: 31% didn't relapse within five years of discharge, and as a group they were much more "socially dependent"--on welfare and needing other forms of support--than the 1947 cohort.

Bockoven's Conclusion:

"Rather unexpectedly, these data suggest that psychotropic drugs may not be indispensable. Their extended use in aftercare may prolong the social dependency of many discharged patients."

Source: Bockoven, J. "Comparison of two five-year follow-up studies," Am J Psychiatry 132 (1975): 796-801.

Rappaport's Study: Three-Year Outcomes

| Medication use (in hospital/after discharge) | Number of Patients | Severity of Illness (1= best outcome; 7 = worst outcome) | Rehospitalization |
|--|-----------------------|--|-------------------|
| Placebo/off | 24 | 1.7 | 8% |
| Antipsychotic/off | 17 | 2.79 | 47% |
| Placebo/on | 17 | 3.54 | 53% |
| Antipsychotic/on | 22 | 3.51 | 73% |

Source: Rappaport, M. "Are there schizophrenics for whom drugs may be unnecessary or contraindicated?" Int Pharmacopsychiatry 13 (1978):100-11.

Rapport's Conclusion:

"Our findings suggest that antipsychotic medication is not the treatment of choice, at least for certain patients, if one is interested in long-term clinical improvement. Many unmedicated-while-inhospital patients showed greater long-term improvement, less pathology at follow-up, fewer rehospitalizations, and better overall functioning in the community than patients who were given chlorpromazine while in the hospital."

--Maurice Rappaport, UCSF, 1978

Loren Mosher's Soteria Project

Study Design

Compared two-year outcomes of first-episode episode patients treated conventionally in the hospital with care in a "therapeutic house" where antipsychotic use was initially delayed, and then prescribed only if patients didn't improve on placebo.

Results:

At end of two years, the Soteria patients had "lower psychopathology scores, fewer [hospital] readmissions, and better global adjustment." In terms of antipsychotic use, 42% had never been exposed to the drugs, 39% had used them temporarily, and 19% had used them regularly throughout the two-year followup.

Conclusion:

"Contrary to popular views, minimal use of antipsychotic medications combined with specially designed psychosocial intervention for patients newly identified with schizophrenia spectrum disorder is not harmful but appears to be advantageous. We think the balance of risks and benefits associated with the common practice of medicating nearly all early episodes of psychosis should be re-examined."

Source: Bola, J. "Treatment of acute psychosis without neuroleptics." J Nerv Ment Disease 191 (2003):219-29.

The NIMH's William Carpenter Raises a Question (1977):

"There is no question that, once patients are placed on medication, they are less vulnerable to relapse if maintained on neuroleptics. But what if these patients had never been treated with drugs to begin with? ... We raise the possibility that antipsychotic medication may make some schizophrenic patients more vulnerable to future relapse than would be the case in the normal course of the illness."

Source: Carpenter, W. "The treatment of acute schizophrenia without drugs." Am J Psychiatry 134 (1977):14-20.

The Dopamine Supersensitivity Theory

The Mechanism:

Antipsychotics block D2 receptors in the brain. As a compensatory response, the brain increases the density of its D2 receptors by 30% or more.

The Consequence:

Two Canadian investigators at McGill University, Guy Chouinard and Barry Jones, reasoned that this made the patient more biologically prone to psychosis, and to worse relapses upon drug withdrawal.

"Neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms ... An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness."

Source: Chouinard, G. "Neuroleptic-induced supersensitivity psychosis," Am J Psychiatry 135 (1978): 1409-10; and "Neuroleptic-induced supersensitivity psychosis," Am J Psychiatry 137 (1980): 16-20.

Drug-Induced Tardive Psychosis

Tardive Dyskinesia:

Dopamine supersensitivity in the neuronal pathway to the basal ganglia is thought to be a primary cause of tardive dyskinesia. This dysfunction of motor movement may remain even after the drugs are withdrawn. Tardive dyskinesia is thought to affect 5% of patients per year treated with standard neuroleptics, with the risk cumulative according to number of years on the drug.

Tardive Psychosis:

Chouinard and Jones reasoned that dopamine supersensitivity in the neuronal pathway to the limbic system leads to a similar dysfunction in that brain region, and thus to tardive psychosis.

Study of Tardive Psychosis:

In 1982, Chouinard and Jones reported that 30% of the 216 schizophrenia outpatients they studied showed sign of tardive psychosis, which meant their psychosis was becoming chronic. When this happens, they wrote, "the illness appears worse" than ever before. "New schizophrenic symptoms of greater symptoms will appear.

Source: Chouinard, C. "Neuroleptic-induced supersensitivity psychos, the 'Hump Course,' and tardive dyskinesia." *J Clin Psychopharmacology* 2 (1982):143-44. Also, Chouinard, C. "Severe cases of neuroleptic-induced supersensitivity psychosis," *Schiz Res* 5 (1991):21-33.

Philip Seeman's D2 HIGH Theory

Atypicals Induce Same Change as Standard Neuroleptics

In 2000, Seeman reported that atypical antipsycotics cause an increase in D2 receptors, just like standard neuroleptics do.

Animal Models of Psychosis

In 2005, Seeman reported that agents that trigger psychotic-like behavior in animals -- amphetamines, angel dust, lesions to the hippocampus, gene-knockout manipulation s-- all cause an increase in D2 receptors that have a "high" affinity for dopamine. These results "imply that there may be many pathways to psychosis, including multiple gene mutations, drug abuse, or brain injury, all of which may converge via D2 HIGH to elicit psychotic symptoms," Seeman wrote.

In this same report, Seeman found that haloperidol and olanzapine both doubled the density of D2 HIGH receptors, and thus cause the very biological abnormality that in animal models had been identified as a pathway to psychosis.

This Leads to Long-Term Treatment Failure

In 2007, Seeman reported on animal studies that demonstrated that this drug-induced dopamine supersensitivity led to "treatment failure over time." Seeman's group concluded that this finding required a rethinking of protocols that emphasized continual drug maintenance.

Source: Seeman, P. "Dopamine supersensitivity correlates with D2 HIGH states, implying many paths to psychosis. Proceedings of the Nat Acad of Science 102 (2005): 3513-18. Samaha, A. "Breakthrough dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time." *J Neuroscience* 27 (2007):2979-86.

Nancy Andreasen MRI Study of 500 Schizophrenia Patients

Findings:

In 2003, Andreasen reported that schizophrenia was a "progressive neurodevelopmental disorder" characterized by "progressive reduction in frontal white matter volume." This decline in brain volumes was seen in the MRI imaging tests.

In 2003 and 2005, she reported that this brain shrinkage was associated with a worsening of negative symptoms, increased functional impairment, and cognitive decline.

In 2011, Andreasen reported that this shrinkage was drug-related. Use of the old neuroleptics, the atypical antipsychotics, and clozapine were all "associated with smaller brain tissue volumes," with decreases in both white and grey matter. The severity of illness and substance abuse had "minimal or no effect" on brain volumes.

Source: Ho, B. "Progressive structural brain abnormalities and their relationship to clinical outcome." Arch Gen Psych 60 (2003):585-94. Andreasen, N. "Longitudinal changes in neurocognition during the first decade of schizophrenia illness." International Congress on Schizophrenia Research (2005):348. Hob, B. "Long-term antipsychotic treatment and brain volumes." Arch Gen Psychiatry 68 (2011):128-37.

WHO Comparative Studies of Schizophrenia Outcomes

Study Design:

Two studies comparing outcomes in India, Nigeria and Colombia with outcomes in the U.S and five other "developed" countries.

Findings:

In both studies, which measured outcomes at the end of two years and five years, the patients in the three developing countries had a "considerably better course and outcome." The WHO researchers concluded that "being in a developed country was a strong predictor of not attaining a complete remission."

Medication Usage:

16% of patients in the developing countries were regularly maintained on antipsychotics, versus 61% of the patients in rich countries.

Source: Jablensky, A. "Schizophrenia, manifestations, incidence and course in different cultures." Psychological Medicine 20, monograph (1992):1-95. See table on page 64 for medication usage.

Martin Harrow's Long-Term Study of Psychotic Patients

Patient Enrollment

- 64 schizophrenia patients
- 81 patients with other psychotic disorders
 37 psychotic bipolar patients
 28 unipolar psychotic patients
 16 other milder psychotic disorders
- Median age of 22.9 years at index hospitalization
- Previous hospitalization

46% first hospitalization

- 21% one previous hospitalization
- 33% two or more previous hospitalizations



Global Adjustment of Schizophrenia Patients







Nervous and Mental Disease 195 (2007):406-14.

Global Adjustment of "Other Psychotic" Patients





"In addition, global outcome for the group of patients with schizophrenia who were on antipsychotics was compared with the offmedication schizophrenia patients with similar prognostic status. Starting with the 4.5-year follow-up and extending to the 15year follow-up, the off-medication subgroup tended to show better global outcomes at each followup."

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Martin Harrow, page 411.
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Five-Year Outcomes for First-Episode Psychotic Patients in Finnish Western Lapland Treated with Open-Dialogue Therapy

| Patients (N=75) | | | | |
|------------------------------------|-----|--|--|--|
| Schizophrenia (N=30) | | | | |
| Other psychotic disorders (N=45) | | | | |
| Antipsychotic use | | | | |
| Never exposed to antipsychotics | 67% | | | |
| Occasional use during five years | 33% | | | |
| Ongoing use at end of five years | 20% | | | |
| Psychotic symptoms | | | | |
| Never relapsed during five years | 67% | | | |
| Asymptomatic at five-year followup | 79% | | | |
| Functional outcomes at five years | | | | |
| Working or in school | 73% | | | |
| Unemployed | 7% | | | |
| On disability | 20% | | | |

Source: Seikkula, J. "Five-year experience of first-episode nonaffective psychosis in open-dialogue approach." *Psychotherapy Research* 16 (2006):214-28.

Depression in the Pre-Antidepressant Era

Who It Affected

Major depression was primarily a disorder of middle-aged and older persons. In 1956, 90% of first admissions to public and private hospitals for depression were 35 years and older.

Prevalence

In the 1930s and 1940s, fewer than one in a thousand adults suffered an episode of clinical depression each year.

Outcomes

People hospitalized for depression could be expected to recover, and longterm outcomes were fairly good. Depression was seen as an episodic illness, and only a small minority of first-episode hospitalized patients (20%) became chronically ill.

The Transformation of Depression in the Modern Era

Upon Introduction of Drugs (1960s and 1970s)

A number of physicians observed that while drug-treated patients were getting better faster, they were now relapsing more frequently. Antidepressants, wrote psychiatrist Nikola Schipkowensky in 1970, were inducing "a change to a more chronic course."

Epidemiologic Studies Document Change in Long-term Course

American Psychiatric Association's *Textbook of Psychiatry*, 1999: It used to be believed that "most patients would eventually recover from a major depressive episode. However, more extensive studies have disproved this assumption." It was now known that "depression is a highly recurrent and pernicious disorder."

Are Antidepressants Depressogenic Over the Long-Term?

"Antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression ... Use of antidepressant drugs may propel the illness to a more malignant and treatment unresponsive course."

--Giovanni Fava, Psychotherapy and Psychosomatics, 1995

The STAR*D Trial Confirms That Depression Runs a Chronic Course Today

Findings from the National Institute of Mental Health's STAR*D study, which was the "largest study" of depression ever conducted:

• Only 38% of the patients properly enrolled in the trial remitted during one of the four stages of drug treatment.

• Only 3% of the patients remitted and then stayed well throughout the 12-month followup. The remaining patients either failed to remit, relapsed during the followup, or dropped out.

Conclusion: "Most individuals with major depressive disorders have a chronic course, often with considerable symptomatology and disability even between episodes."

Source: Pigott, E. "Efficacy and effectiveness of antidepressants." Psychother Psychosom 79 (2010):267-79.

Depression in the Netherlands

(Over the course of ten years)

First episode treated with drugFirst episode treated without drug



Source: E. Weel-Baumgarten, "Treatment of depression related to recurrence," J Clin Psychiatry & Therapeutics 25 (2000):61-66.

One-Year Outcomes in WHO Screening Study for Depression



Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." British Journal of General Practice 48 (1998):1840-44.





Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.



Antidepressants Lessen the Long-Term Benefits of Exercise

| Treatment during first 16 weeks | Percentage of patients in remission at end of 16 weeks | Percentage of patents who relapsed in following six months | Percentage of all patients depressed at end of ten months |
|---------------------------------------|---|--|--|
| Zoloft alone | 69 % | 38% | 52% |
| Zoloft plus exercise | 66% | 31% | 55% |
| Exercise alone | 60% | 8% | 30% |

Source: Babyak, M. "Exercise treatment for major depression." *Psychosomatic Medicine* 62 (2000):633-8.

The Bipolar Boom

Annual Prevalence in the Pre-Lithium Era

•One in 3000 to one in 10,900

Prevalence Today:

• One in 50 adults

Bipolar Outcomes in the Pre-Drug Era

Swedish Study, 1945

103 manic patients

Recovered Patients

Chronically ill



Source: Lundquist, G. "Prognosis and course in manic-depressive psychoses." *Acta Psychiat Neurol*, Supp. 35 (1945):7-93.

Functional Bipolar Outcomes in the Pre-Drug Era



Outcomes for 100 manic patients first hospitalized in U.S., 1935-1945, and followed for 30 to 40 years. A good rating for each category meant that the patient was married or widowed, owned home or lived with family members, was employed or had retired, and had no psychiatric symptoms. Seventy percent of the patients had good functional outcomes, and half were asymptomatic. Source: Tsuang, M. "Long-term outcome of major psychoses." *Arch Gen Psych* 36 (1979):1295-1301.

Summary of Outcomes in Pre-Drug Era

There is "no basis to consider that manic depressive psychosis permanently affected those who suffered from it. In this way, it is of course different from schizophrenia." While some people suffered multiple episodes, each episode was usually only a "few months in duration" and "in a significant number of patients, only one episode of illness occurs." Once patients recovered, they usually had "no difficulty resuming their usual occupations."

> --George Winokur, Washington University, 1969 Manic Depressive Illness

Gateways to Bipolar Today

- Illicit drugs (marijuana, cocaine, hallucinogens, etc.)
- Stimulants and antidepressants
- Expanded Diagnostics

The Antidepressant Pathway

In 2004, Yale University investigators reviewed the records of 87,290 patients diagnosed with depression or anxiety between 1997 and 2001, and those treated with an antidepressants converted to bipolar at the rate of 7.7% per year, which was three times greater than those not exposed to the drugs. As a result, 20 to 40% of unipolar depressed patients in the U.S. who stay on antidepressants long-term convert to bipolar illness.

Source: A. Martin. "Age effects on antidepressant-induced manic conversion," Arch of Pediatrics & Adolescent Medicine 158 (2002):773-80.

Fred Goodwin, former director of the National Institute of Mental Health, 2005:

"If you create iatrogenically a bipolar patient, that patient is likely to have recurrences of bipolar illness even if the offending antidepressant is discontinued. The evidence shows that once a patient has had a manic episode, he or she is more likely to have another one, even without the antidepressant stimulation."

Worsening Long-term Course of Bipolar Illness in Drug Era

"The general impression of clinicians today is that the course of recurrences of manicdepressive illness has substantially changed in the last 20 years. The recurrences of many patients have become more frequent. One sees more manias and hypomanias . . . more rapid cyclers and more chronic depressions."

--Anthansious Koukoulos, 1983

The Modern Course of Bipolar Illness

- More recurrent episodes and more rapid cycling
- Low-level depression between episodes
- Only 33% enjoy good functional outcomes (compared to 70% to 85% in pre-drug era)
- Long-term cognitive impairment (which wasn't seen in pre-drug era)
- Physical problems related to long-term medication use
- Risk of early death

Experts Recognize The Decline in Bipolar Outcomes

Carlos Zarate, head of NIMH Mood Disorders Program, 2000:

"In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment."

Ross Baldessarini, Harvard Medical School, 2007.

"Prognosis for bipolar disorder was once considered relatively favorable, but contemporary findings suggest that disability and poor outcomes are prevalent, despite major therapeutic advances."

Fred Goodwin, 2008

"The illness has been altered. Today we have a lot more rapid cycling than we described in the first edition [of his book, *Manic Depressive Illness*], a lot more mixed states than we described in the first edition, a lot more lithium resistance, and a lot more lithium treatment failure than we described in the first edition. I The illness is not what Kraepelin described any more."

The Transformation of Outcomes for Major Mental Disorders in the Modern Era

Summary of long-term outcomes literature

• Research shows that antipsychotics worsen the long-term course of schizophrenia. The drugs lower recovery rates, and cause brain changes associated with increased biological vulnerability to psychosis, functional impairment, and long-term cognitive decline.

• Depression has been transformed from an episodic disorder into a chronic illness, with much higher disability rates

• Use of illicit drugs, stimulants and antidepressants have helped create a 100-fold increase in the prevalence of bipolar illness (in U.S.)

• Functional outcomes for bipolar illness have dramatically deteriorated in modern era.

Rethinking Psychiatric Care

"The majority of mental illnesses, especially the most severe, are largely self-limiting in nature if the patient is not subjected to a demeaning experience or loss of rights and liberties."

-- Samuel Bockoven, 1975

A. The field needs to investigate and re-discover the long-term course of major mental disorders prior to the pharmacotherapy era, as epidemiological studies from that era tell of people regularly recovering from acute episodes of mental illness, including psychosis, and often staying well for long periods of time, or even indefinitely.

B. The field needs to incorporate the long-term outcomes literature into its medication protocols, and thus develop protocols that involve using the medications in a more selective, cautious manner. These protocols may involve delaying initial use of medications, and trying to minimize long-term use. (See Western Lapland's "open dialogue" program.)

Soaring Costs May Drive this Rethinking of Care

- In 2001, the U.S. spent \$85 billion on mental health services
- In 2008, the U.S. spent \$170 billion on mental health services
- In 2015, the U.S. is expected to spent \$280 billion on mental health services
- The public, through its Medicaid and Medicare programs, covers 60% of this cost
- These figures do not include the costs the SSI and SSDI disability programs. The lifetime cost of caring for an 18-year-old who goes onto disability for mental illness can be expected to exceed \$2 million.

Source: Mundell, E. "U.S. Spending on mental health care soaring," *HealthDay*, Aug. 6, 2009. Mark, T. "Mental health treatment expenditure trends, 1986-2003." *Psychiatric Services* 58 (2007):1041-48.