

**SECOND GENERATION
ANTIDEPRESSANTS AND
ANTIPSYCHOTICS**

MOVING UPSTREAM

Deaths can be quantified, but the sub
lethal side effects manifest as
PHARMACOLOGICAL
IATROGENESIS

**Yolande Lucire
PhD, MB BS DPM FRANZCP**

Forensic Psychiatrist

Poster from 40th RANZCP CONFERENCE, Sydney,
May 2005.

The NSW Government's Plan for
Mental Health Services

informs us of **OUR ACHEIVEMENTS**,
namely

Since June 2001, an **additional 257
mental health beds have opened.**

By June 2005, an additional 40 beds
will have opened.

Does presiding over increasing
need for mental health care
represent an achievement?

THE INVISIBLE PLAGUE: THE RISE OF MENTAL ILLNESS FROM 1750 TO THE PRESENT. (Rutgers University Press. 2002)

E. Fuller Torrey and Judy Miller ask why insanity , once considerably less than one case per 1000 of population, reached epidemic proportions. 0.68/1000 in 1807 to 7.13/1000 in 1961.

SUGGESTED CAUSES INCLUDE
AVAILABILITY OF FACILITIES
ACCUMULATION AND AGED PATIENTS
GENETIC
INDUSTRIAL REVOLUTION AND AND URBANISATION
STRESS
DIET
ALCOHOL
TOXINS
MEDICAL CARE#
INFECTIONS AGENTS
 syphilis
 the polio model the vaccination model
 the pet cat model

#Norman Sartorius suggested the less fit infants survived because of better obstetric care

I pose another causal hypothesis:

IATROGENESIS,

specifically

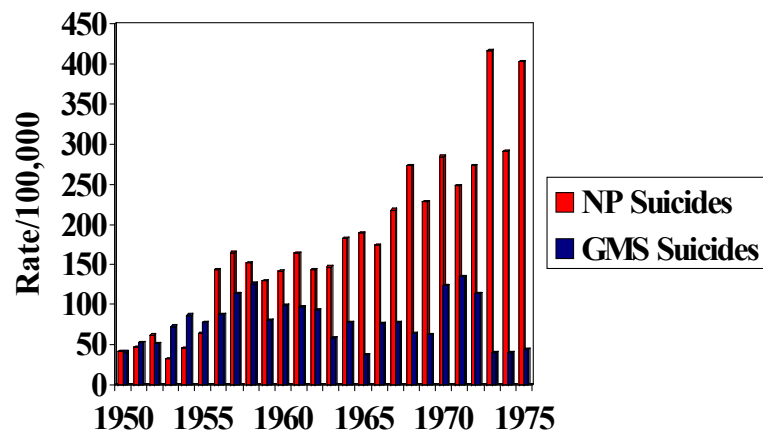
PHARMACOLOGICAL IATROGENESIS.

Is it possible that the remedies we provide for minor disorders are causing major ones?

What about the alternatives?

2

SUICIDES IN V.A. HOSPITALS



From these figures it can be seen clearly that the natural rate of suicide in schizophrenia was indistinguishable from that of the rest of the population – see the rates for 1950-1955, when Thorazine was introduced. The best figures today for the natural rate of suicide in schizophrenia suggest that the rate is little different from that of the normal population.

Healy D, Harris M, Tranter R, Gutting P, Austin R, Jones-Edwards G, Roberts AP (in press). Lifetime Suicide Rates in the Course of the Treatment of Schizophrenia in North Wales: Two Cohorts 1875-1924 & 1994-1998. *British Journal of Psychiatry*.

Psychiatric drugs are not alone in causing morbidity. In the United States, the fourth highest cause of death after heart disease, cancer and strokes are the adverse drug reactions.

ADEs are responsible for over 105,000 deaths per year and affect many more with their sublethal side effects.

If one adds improperly prescribed drugs and those taken incorrectly, adverse drug events (ADEs) become the third highest cause of death.

Recognition of these adverse drug reactions and withdrawal of the offending substances

can prevent misdiagnosis and potentially severe long term iatrogenic disorders

Lazarou J, Pomeranz BH and Corey PN: Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. *JAMA*, 279:1200-1205, 1998. Total Recall. Four Corners. ABC. 10 April 2005 on Vioxx.

Akathisia is a subjective desire to be in constant motion.

A manifestation of drug sensitivity, it may be confused with psychotic agitation, and incorrectly treated by increasing the dose of the offending medication.

The symptom subsides when the offending medication is discontinued and replaced by another one, better tolerated by the patient.

Source: Modern Synopsis of Psychiatry III, Kaplan and Saddock.

1981 edition. And all since.

SSRI-induced akathisia is in the Diagnostic and Statistical Manual (DSM IV TR) at 333.99

Teicher, Glod and Cole (1993) suggested **9 “clinical mechanisms” by which SSRIs can induce or exacerbate suicidal tendencies** by causing the following:

- (a) **energizing depressed patients to act on pre-existing suicidal ideation;**
- (b) **paradoxically worsening depression;**
- (c) **inducing akathisia with associated self-destructive or aggressive impulses;**
- (d) **inducing panic attacks;**
- (e) **switching patients into manic or mixed states;**
- (f) **producing severe insomnia or interfering with sleep architecture;**
- (g) **inducing an organic obsessional state;**
- (h) **producing an organic personality disorder with borderline features;**
- (i) **exacerbating or inducing (EEG) or other neurological disturbances.**

Teicher MH, Glod CA, Cole JO. The emergence of fluoxetine- induced suicidality. Drug Safety 1993;8(3):186-212

Suicidal ity, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis *

Peter R. Breggin

101 East State Street, No. 112, Ithaca, NY 14850, USA

Abstract. Evidence from many sources confirms that selective serotonin reuptake inhibitors (SSRIs) commonly cause or exacerbate a wide range of abnormal mental and behavioral conditions. These adverse drug reactions include the following overlapping clinical phenomena: a stimulant profile that ranges from mild agitation to manic psychoses, agitated depression, obsessive preoccupations that are alien or uncharacteristic of the individual, and akathisia. Each of these reactions can worsen the individual's mental condition and can result in suicidality, violence, and other forms of extreme abnormal behavior. Evidence for these reactions is found in clinical reports, controlled clinical trials, and epidemiological studies in children and adults. Recognition of these adverse drug reactions and withdrawal from the offending drugs can prevent misdiagnosis and the worsening of potentially severe iatrogenic disorders. These findings also have forensic application in criminal, malpractice, and product liability cases.

(1) The production of a **stimulant continuum** that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progresses toward more severe agitation, aggression, and varying degrees of mania. **Mania** or manic-like symptoms include **disinhibition, grandiosity, sleep disturbances, and out-of-control aggressive behaviour**, including cycling into depression and suicidality.

(2) The production of a combined state of **stimulation and depression – an agitated depression** – with a high risk of suicide and violence. Often the overall **depression is markedly worsened**.

(3) The production of **obsessive preoccupations** with aggression against self or others, often accompanied by a worsening of any pre-existing depression.

(4) The production of **akathisia**, an inner agitation or jitteriness that is usually (but not always) accompanied by an inability to stop moving. It is sometimes described as **psychomotor agitation or restless leg syndrome**.

Those at risk of suicide are agitated, in turmoil, nervous, sleepless, pacing, energized, almost manic, and they reject their obsessive suicidal thoughts as 'strange', 'weird,' 'not me'.

This can go on for weeks or can turn into suicide unpredictably in a matter of minutes.

The traditional suicidogenic triad

1) **akathisia,**

(2) **emotional blunting,** also called psychic numbing **"I cannot feel anything, do not care"** and/or

(3) **psychotic decompensation**

In turmoil, feeling numb as if nothing matters, and feeling one is going mad

•Teicher and Cole, 1993 Healy, Langmaak, and Savage, 1999;

SSRI overdoses are less likely to be fatal, but Efexor XR is as toxic in overdose and amitriptyline..

SSRI suicides tend to be violent:

**Akathisiacs are thinking about hanging, drowning, shooting, jumping, stabbing or cutting,
or
dying on a railway,**

immolation, burning, electrocution, or deliberate road accidents.

Trying to get police to shoot them, some cut their throats and self mutilate in public, usually using alcohol as well.

I have seen deliberate self harm associated with semi-delirium characterised by violent blood-laden, or sexual abuse hallucinations, coming out of nowhere, sometimes interpreted as "memories" 'recovered' out of the blue.

Sachdev and others report 'sexual craving'

SECOND GENERATION DRUGS DID NOT PERFORM WELL IN CLINICAL TRIALS

Kahn found 77 suicides in 48,277 participants in SSRI trials.

Khan then reviewed 71,604 participants in FDA clinical trials treated with **ANTIPSYCHOTICS, SSRIs AND ANTICONVULSANTS** and found a rate of 757 suicides/ 100,000 PEYs (participant years) or 715 per 100,000 participants.

That is 68 times the population rate, enormous.

Kahn's research further revealed that nearly **4% of drug-trial participants attempted suicide the following year.**

4000/100,000 That suggested that these drugs may affect people for a while after they are stopped.

Khan, A., Khan, S., Kolts, R., & Brown, W. (2003). Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry*, 160(4), 790-792

Am J Psychiatry. 2003 Apr;160(4):790-2.

The do not do very well in the field either. RR risk of sudden death v sugar pills is 1.7. So:

FDA Talk Paper April 11, 2005

•FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients

•The Food and Drug Administration (FDA) today issued a public health advisory to alert health care providers, patients, and patient caregivers to new safety information concerning an unapproved (i.e., “off-label”) use of certain drugs called “atypical antipsychotic drugs.”

•... have shown a higher death rate associated with their use compared to patients receiving a placebo (sugar pill).

•Today’s advisory applies to such antipsychotic drugs as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Risperdal (risperidone), Clozaril (clozapine) and Geodon (ziprasidone). Symbyax

SECOND GENERATION ANTIPSYCHOTICS MAY ALSO BE CULPABLE.

David Healy analysed the FDA trials that got the atypical antipsychotics licensed. They are now publicly available on the FDA website.

The regulator, the FDA, just did not notice, in the late 1980s that 1 in every 145 subjects that entered the trials for olanzapine, risperidone, and ziprasidone died.

Most, but not all by suicide. Strokes were very common. Coroners have not been told there is an FDA advisory about sudden death in elderly patients.

Zyprexa (Olanzapine) trials had the highest rate of suicide in clinical trial history. 84, i.e. 1 in 35 - had serious side effects.

Suicide and Suicide Attempts in Clinical Trials of Antipsychotic Agents submitted to the FDA

	Number of Patients	Patient Exposure Years	Number of Suicides	Number of Suicide Attempts
Risperidone	2,607	858	9	43
Comparator	621	71	1	5
Placebo	195	15	0	1
Olanzapine	2,500	1,122	12	N/A
Comparator	810	193	1	N/A
Placebo	236	27	0	N/A
Quetiapine	2,523	1,103	1	4
Comparator	420	52	0	2
Placebo	206	15	0	0
Sertindole	2,194	1,024	5	20
Comparator	632	129	0	2
Placebo	290	27	0	1
Ziprasidone	2,993	1,189	6	N/A
Comparator	951	383	1	N/A
Placebo	424	82	0	N/A
Total				
New Antipsychotic	12,817	5,296	33	72
Comparator	3,434	828	3	10
Placebo	1,351	166	0	2

Only 5 Zyprexa trials were undertaken to underpin its use in Schizophrenia
50% of enrolled participants did not complete six week trials because of side effects.
1 in 208 committed suicide.

There were 3 Risperdal trials.
50% did not complete.
1 in 250 committed suicide.

Trial 1: 160 patients, 6 weeks
50% did not complete
FDA: "equivocal"
Trial 2: 523 patients - 45% did not complete.
FDA: 'multiple doses of risperidone compared with a single dose of haloperidol -biased)
Trial 3: 1557 subjects 5 countries

To get psychotic patients for \$10-\$25,000 each, Borison and Diamond took their schizophrenics off Haloperidol to generate active psychosis, then compared one dose of haloperidol to many of the atypical. They went to jail for ripping off a university. Their work is still cited.

All clinical trials (with strategic information omitted) are now available on FDA website.

12 suicides but no other suicidal acts?
Whom are they kidding?
EVERYONE, and very successfully.

Enter: ENDORSEMENT SCIENCE

5 trials of Zyprexa for schizophrenia generated 234 ghost-written articles by prominent opinion leaders and many company summaries.

None of these publications yields a true picture of the drop out rate, side effects or risk of suicide or suicidal acts on Zyprexa.

RISPERDAL and ZYPREXA were promoted on the cover of Time Magazine, The Post, Washington Times and New York Times.

The Dopamine Theory of Schizophrenia was alive and well in those endorsements.

from David Healy, unpublished. Details from Professor Clive Adams of the Cochrane Centre for Schizophrenia, Leeds, October 2004.

The suicide rate for these trials, on a time-adjusted basis, was two to five times the norm for schizophrenics.

But the literature has already told us, provided you can read it backwards that Zyprexa causes suicide.

Meltzer *et al*;. Clozapine reduces the risk of suicide compared with Zyprexa by 75% .

(Those treated with Clozaril already have a higher suicide rate than untreated.)

ARE WE LOOKING AT ANOTHER VIOXX-STYLE DECEPTION?

Did Merck not tell us that Naprosyn protected against of heart attacks, when compared with Vioxx? When Vioxx caused the heart attacks and they knew!

Which causes? Which protects? Check out the FDA trials.

Meltzer, H.Y., et al., Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial Arch Gen Psychiatry.2003 Jul;60(7):735]. Archives of General Psychiatry, 2003. 60(1): p. 82-91.(5 papers like this)

According to the Mental Health plan, the suicide rate in NSW has declined from 15.1 per 100,000 persons in 1997 to 9.5 per 100,000 persons in 2003, the lowest rate of suicide in Australia.

ARE MENTAL HEALTH SERVICES A ADDING TO OR SUBTRACTING FROM THIS THIS FALL? Look a the evidence:

PROF RAPHAEL: 2003

About **400** mentally ill patients in Oz under mental health care, **commit suicide each year.**

People fronting at hospital emergency departments for psychiatric treatment has **DOUBLED** in the past decade and presentations are more violent.

. Various DoH statistics NSW, Victoria, Western

Mental Health suicide rate 48 hours after discharge, is **100 times** the rate for the general population. For patients with 'depression', it is up to 500 times.

Murders by 'mentally disordered' persons (not in state Mental Health care) are running at three a month, having nearly doubled recently from 20 victims in 2000-'01 to 36 in 2001-'02. (BOSCAR)

Ross Kalucy reports a similar phenomenon at Flinders Medical Centre in South Australia.

Flinders Medical Centre mental health presentations at Emergency Department

1994/1995 it was 248 (double or treble this as it was one of several hospitals then) and in 2002/2003 it was 1838 (not counting overdoses)

Source: Kalucy R Thomas D King D Changing Demand for Mental Health Services RANZCP Journal, January February 2005 74-80

WESTERN AUSTRALIA

Annual deaths from suicide among mental health patients doubled from 1980 to 1998.

45% of suicides occurred in people who had used mental health services.

- The majority had one short contact following a suicide attempt and had committed suicide before receiving any follow-up.

Suicide rates were seven times higher in people diagnosed with "mental illness," and the number so diagnosed was increasing as well.

The rate of suicide in people with mental illness has been increasing over the period 1990-98, and the increase in that rate almost entirely explains the net increase in the total West Australian suicide rate.

Coglan R, Lawrence D, Holman, D. A., & Jablenski, A. (2001). *Duty to Care: Physical Illness in People with Mental Illness*: Department of Public Health and Department of Psychiatry and Behavioral Science, University of Western Australia.

From 1990 to 2002, antidepressant use increased by 352%, to reach 51.5 DDDs/1000/day

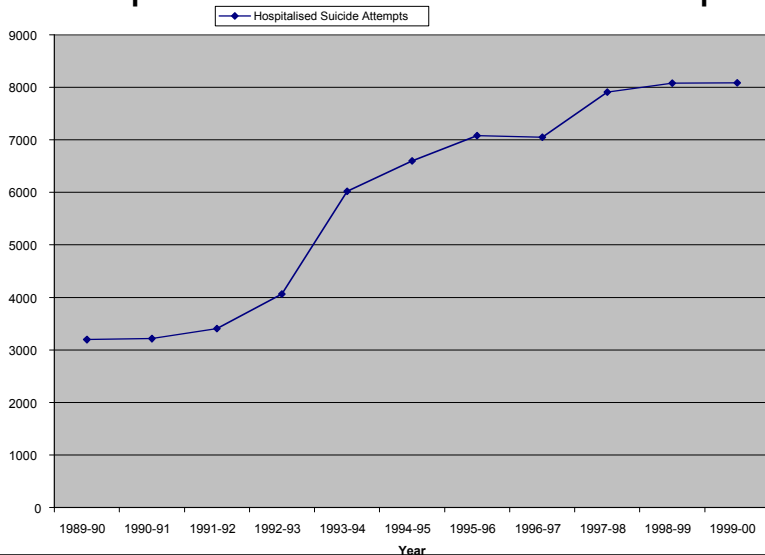
In this same period, 1990 and 2002, Suicides of persons under Mental Health Care (in NSW alone) increased from 24 to over 156.

Just about 350%

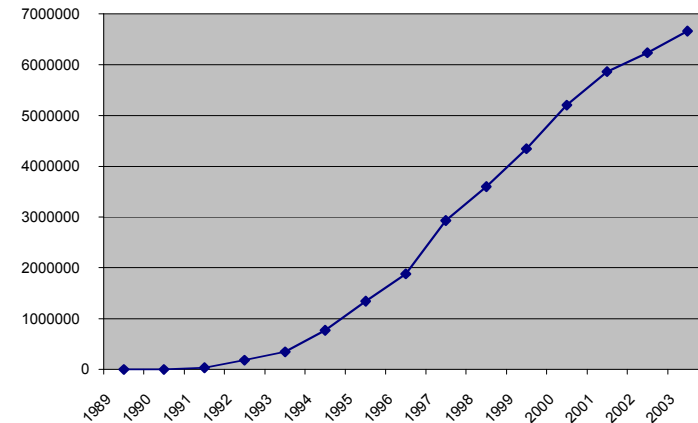
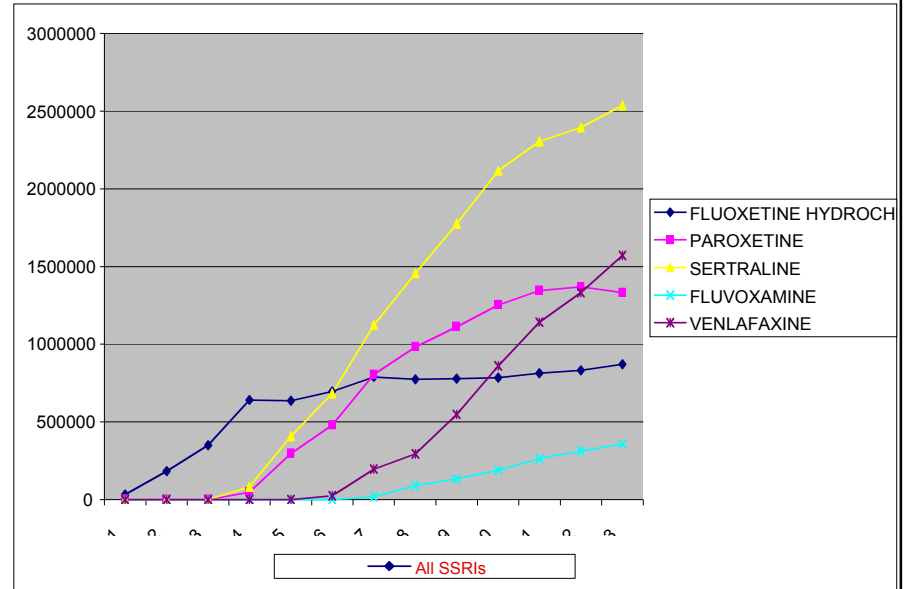
This becomes an empirical question for coroners who will have toxicological results from all of these deaths.

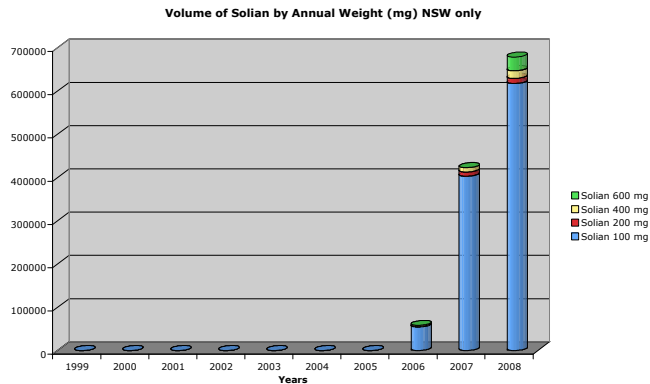
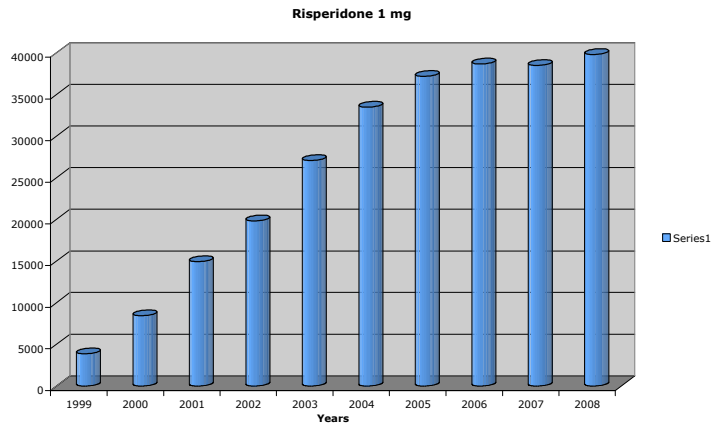
'Separations' for suicide attempts increased from 3211 to 8090 in NSW from 1989 to 2002.

'Separations' for suicide attempts

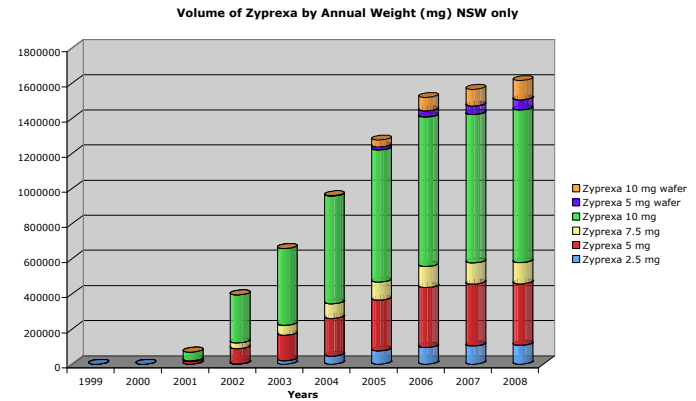


ANTIDEPRESSANT PRESCRIBING

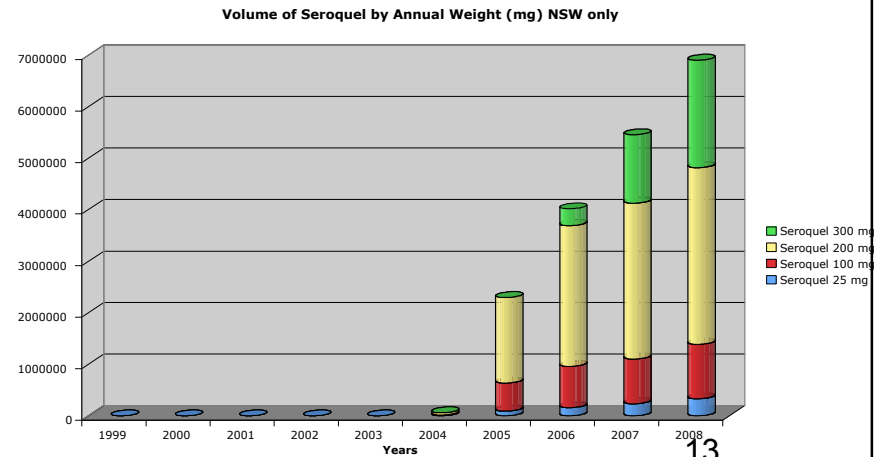




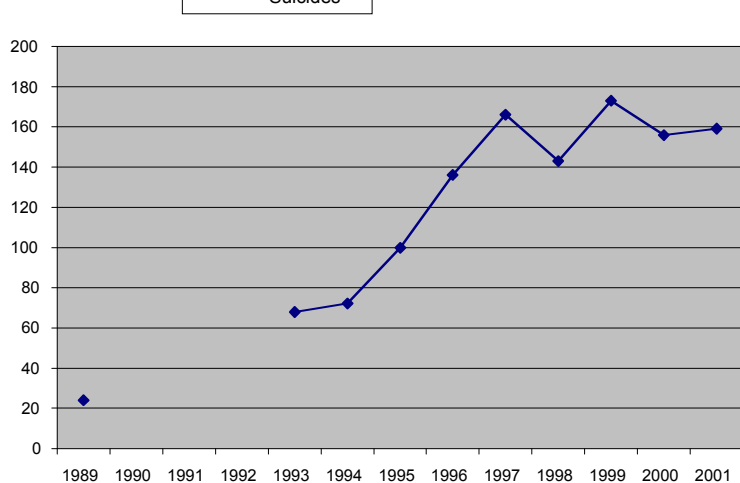
These figures are for NSW. Seroquel was not suicidogenic in FDA trials. It does cause akathisia and withdrawal akathisia in the vulnerable.



These pictures do not tell the full story.. To understand this one needs to know how many new persons started SSRIs and Atypicals these drugs at any dose and how many came off them. Starting and stopping are danger periods for both. The HIC cannot provide this data.



Suicides under Mental Health Care NSW



Graph of Sentinal Events Committee Report. NSW Suicides under Mental Health Care. 1993 to 2002.

As Mental Health Services prescribe antidepressants and antipsychotics, it is unlikely they are contributing to a fall in suicide rates.

- The Sentinel Events Committee chaired by the Hon. Professor Emeritus Peter Baume AO, charted the rising mental health suicide numbers since 1993. Dr Bill Barclay AM looked at 9 Homicides by patients under Mental Health care.
- Tracking Tragedy: Report of NSW Mental Health Sentinel Events Committee

Year	Suicides in NSW	Suicides in mental health care	Percent fall suicides
1993	676	68	10%
1994	798	72	9%
1995	747	100	13%
1996	811	136	17%
1997	946 rate 15.1/100k	166	18%
1998	827	143	17%
1999	846	173	20%
2000	738	156	21%
2001	775	159	21%
2002	?? rate 0.5/100k		
2003		128	

How common are serious adverse events (hospitalisations) with antidepressants?

A 2001: Yale: 8% of patients admitted **'may suffer'** from SSRI-induced mania or psychosis.

Preda A, MacLean RW, Mazure CM, Bowers MB (2001). Antidepressant associated mania and psychosis resulting in psychiatric admission. J Clinical Psychiatry 62, 30-33

Higher levels of prescribing in OZ and include **agitation, suicidal and homicidal thoughts and attempts in patients on these drugs,**

It is 2 or 3 admissions a week into 21 beds and this profile accounts for 20 to 30% of admissions.

I charted 600 consecutive discharge summaries for 18 months, and found 150 admissions worth reporting to ADRAC, (not including psychosis or mania) and 42 more in the next 4 months.

I looked for suicidal and homicidal violence and acts, where Second generation antidepressants and atypicals were being used.

The patients whom I assessed (about half of them) had akathisia with the spectrum of side effects described earlier.

All suicidality remitted when the side effects of the antidepressant, atypical or combination of them, were discussed with the patient and carefully withdrawn.

Historians of psychiatry will recall the trajectories of wonder drugs cocaine, bromide, barbiturates, meprobamate mandrax benzodiazepines. It took years before their adverse effects were discovered and acknowledged. Each left a residue of addicts.

They were often on large doses of antidepressants combined with antipsychotics, the latter having been prescribed when antidepressants had caused voice hallucinations or visions.

Suicidal and homicidal ideation were obsessive, intrusive violent and unwelcome. 'Not me.' 'Weird'

They were not the usual suspects, not borderlines, but ordinary people caught up in our gung ho 'obligation' to treat a new socially constructed condition labelled 'depression' the diagnosis of which has increased a thousandfold since a 'cure' became available for it.

Few, if any, had been put on this medicine for serious depression. Many had got worse. Some had suffered like this for up to nine years, undiagnosed.

Where akathisia is suspected, delirium might coexist,

Is the patient telling you she is 'seeing things, hearing things' or constructing a system of delusions around her hallucinations?

The former is recurrent toxic psychosis, which is a delirium,

The latter is schizophrenia.

This is not trivial.

The treatment for schizophrenia induces akathisia in the sensitive.

Amphetamines and cannabis cause akathisia and toxic psychosis which is a delirium.

Drugs do not cause schizophrenia even though their effects mimic it.

Could this patient's condition be iatrogenic? Iatrogenic Depression, Mania, OCD, Panic Disorder, sleep disorder. Iatrogenic late onset or acute borderline traits?

You have to know the natural history of all of those conditions, at what age they start, and make a fine diagnosis. Akathisia is always iatrogenic.

Who will warn the prescriber? Some manufacturers have now sent misspelt faxes to doctors.

Product inserts have not improved. Others have quietly upgraded information in MIMS.

But who understands akathisia?

The Adverse Drug Reactions Advisory Committee (ADRAC) has not yet passed on the FDA's warnings of March 22, 2004..

But promised me they would, and then say they will not. Advice from the RANZCP is cited.

The madman of our nightmares is not a schizophrenic but an akathisiac

All over the world, clinicians are reviewing all their suicidal patients and finding among them chronic akathisia subjects behaving like borderlines, their lives a living hell, battling a death wish, violent, suicidal, toxic and psychotic, with homicidal impulses, ego-alien outbursts of violence, unable to articulate internal agitation, her condition attenuated, but never fully relieved, by co prescribed sedatives or worse, self-administering alcohol or whatever else is available.

The greatest satisfaction I have had in my 38 years as a psychiatrist has come from success in giving lives back to those who have suffered from this totally debilitating and unrecognised iatrogenic disorder for up to eight years

If the FDA figures are right, and some of these are akathisia cases,

the relative risk of using atypicals and SSRIs together has to be so high as to be off the graph.

Some doctors are not aware that hallucinations are a common side effect of SSRIs, and they introduce an atypical.

This spells AKATHISIA, sooner rather than later.

- Much literature was published in the 1970s and 1980s on suicide and homicide associated with akathisia,

induced by traditional neuroleptics,

75 suicides in one paper,
6 homicides in another.

Many papers by Theodore van Putten, Jerome Schulte, M. Katherine Shear cited in *Mad in America* Robert Whittaker Perseus Publishing 2002. Medline Search, akathisia suicide violence

This is about risk management.

If they are making suicide attempts on SSRIs the prescriber has increased the RR of that behaviour statistically by 2.2 minimum to 10 or more.

If they are taking both, the risk is immeasurably higher. They interact and both groups are neurotoxic.

Withdrawal can be tricky and that's when we lose them, if we are not alert and the patient is not warned

If the patient is not hospitalised for obsessive and sudden urges. Looking for hooks to hang from, electric sockets to electrocute themselves, windows to jump from.
If relatives are not warned.

Patients will tell only if you explain why you need to know.

I have had up to 18 akathisia patients on a 21 bed ward in a fortnight in August and they all needed to be there. We lost the 19th one I and should not have done.

Zyprexa was a blockbuster and one of the ten most prescribed drugs in Australia in 2002. This means that it is being given, off label' to people who do not suffer from schizophrenia.

The Melbourne Age reported on a Victorian psychiatric unit that suffered 13 suicides in 13 months, in 2002-3. (Anonymous: (2004, March 17). Critical condition The Age. Melbourne.

Suicide risk is more than 1 in 500.

**1 in 500
too rare for clinicians to see as being abnormal.
They need advice from suicide epidemiologists and statisticians.
Like the Jicks.**

**1 in 500
is well above Rogers and Whittaker's,
1 in 14,000
and demands a duty to warn of a catastrophic side effect**

Litigation arising out of these hazards against health departments and doctors could produce another medical indemnity crisis.

The problem can be diverted to the source, the PhaRMAs, which collectively have deceived the Commonwealth, taxpayers, patients and prescribers

Not only the companies, but their Chief Executives and Boards, should be held responsible for ensuring the reliability of prescribing information and be held liable for the consequences of having provided prescribers and patients with information which is false or misleading, misrepresented or intentionally withheld.

In 1974, Ivan Illich popularised a term,

iatrogenesis, for the 'new' epidemic of doctor-made disease

it is **clinical**, when sickness is caused by medical care;

social, when health policies reinforce ill health; and

structural when the medical profession undermines the confidence of people in their own ability to recover

Illich I. Limits to Medicine: The Expropriation of Health. London: Penguin Books, 1975.

The World Health Organization, bearing information that psychiatric services increase suicide rates in developing countries, has been trying to tell the west for decades that problems occur when people take psychotropic drugs for too long or come off these drugs suddenly and not gradually.

They do not prevent relapse.
Rather they increase relapses.

Suppl. 20 (1992) cited in Mad in America Robert Whittaker Perseus Publishing 2002

In his critique of Illich, Vicente Navarro wrote

that the responsibility for iatrogenesis did not lie with the medical profession

but with the powerful corporate classes which decide what and how health care is delivered.

The corporate classes control governments, insurers and Pharmaeutical companies who, in turn, profoundly influence the behaviour of trusting doctors.

Navarro's somewhat unpopular views of medical practice have been amply demonstrated in the history of big Pharma.

Vicente Navarro: the Industrialization of Fetishism, a Critique of Illich in Medicine under Capitalism.