A REPORT ON THE USE OF PSYCHIATRIC MEDICATIONS THEIR SAFETY AND EFFICACY

Providing a Detailed Meta-Analysis

A Non-Profit Support For the Mentally Ill

A REPORT ON THE USE OF PSYCHIATRIC MEDICATIONS AND THEIR EFFECTS

EXECUTIVE SUMMARY

- Research into the use of medications in the U.S. demonstrates that over 200,000 deaths are created within the hospital setting annually. Additionally over 2.1 million serious injuries take place. These occur from properly prescribed medications. Adverse Drug Reactions (ADRs) make these reactions between the fourth and sixth leading cause of death. In the year 2000 medication ADRs, drug related morbidity and mortality exceeded $177.4 billion in the ambulatory setting in the United States. The largest component of this total cost was associated with drug related hospitalizations. Since 1995, the cost of drug related problems have more than doubled.

- Data from numerous studies are demonstrating that clinical efficacy is not sufficient to warrant the risk of prescribing some of the most commonly used psychiatric medications.

- Extensive research shows that psychiatric medications are actually producing serious patient illness and hospitalizations.

- Relapse into hospital for a psychiatric patient is a common event in spite of continual medication maintenance treatment. Data shows a ***5-year relapse rate to be well over 70%*** in spite of optimal pharmacological treatment.

- Of great concern is the growing evidence that many psychiatric medications raise the risk of cancer, addiction, and suicide. For instance, a woman taking certain psychiatric medications ***more than doubles her risk of ovarian cancer.*** Indeed, the use of one antidepressant Paxil (Paroxetine) is a ***greater risk factor for cancer than is smoking***.

DETAILED ANALYSIS

ADVERSE DRUG REACTIONS (ADRs)

In 1998 researchers at the University of Toronto reviewed adverse drug reactions (ADRs) in U.S. hospitals. Estimations using 1994 data showed that there were 106,000 fatalities and over 2.1 million serious complications requiring hospitalization due to ADRs. "The study excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs." These deaths or injuries resulted from properly prescribed medications. The researchers stated, "The incidence of serious and fatal ADRs in U.S. hospitals was found to be extremely high." 106,000 people had fatal ADRs while hospitalized, "making these reactions between the **fourth and sixth leading cause of death**."[1]

In 1995 Johnson and Bootman published a study in the *Archives of Internal Medicine* in which they stated, "drug related morbidity and mortality was estimated to cost $76.6 billion in the ambulatory setting in the United States."

Based on 1992 figures, these same investigators stated that "the number of admissions that was estimated from the model suggested that **28.8% of all hospital admissions were a result of drug – related morbidity and mortality…** Our results indicate that drug – related morbidity and mortality should be considered one of the leading diseases in terms of resources consumed…The estimated number of deaths owing to ADRs (drug related problems) ranged from **79,159 to 198,815 deaths**." [2]

A 2001 update to the 1995 Johnson – Bootman study completed by Ernst and Grizzle at the

University of Arizona, concluded that overall, the cost of U.S. drug related morbidity and mortality exceed $177.4 billion in the year 2000 with over **200,000 deaths** created annually. The largest component of this total cost was associated with drug related hospitalizations. Since 1995, the cost of drug related problems have more than doubled "Strategies for preventing drug-related morbidity and mortality are urgently needed." [3]

Table 1. Direct Costs of Medical Conditions United States [4]

Condition	Source	$-billion
Non-Insulin – Dependent Diabetes	Wolf et al. 1994	15.5
Obesity (1990)		45.8
Diabetes (1990)	Amer.Diabetes Assoc. 1993	45.2
Cardiovascular Disease (1992)	American Heart Association 1993	117.0
Drug-Related Morbidity and Mortality (1994)	**Johnson & Bootman**	**76.6**
Drug Related Morbidity and Mortality (2000) [3]	**Ernst & Grizzle**	**177.4**

The Institute of Medicine, a section of the prestigious National Academy of Sciences, reported in 1999 that as many as 98,000 people die every year in U.S. hospitals from medical errors. Many deaths are attributable to the use of medications. The report stimulated a swift response from Congress when the US President ordered congressional hearings into the matter.[5] [6]

Applying the above data to Canada, based on U.S. – Canadian population figures, approximately 20,000 deaths per annum occur from ADR's at a cost of 17.7 billion dollars.

IS CLINICAL EFFICACY A REALITY?

In the past two years there have been a number of media stories on the extreme side effects of certain psychiatric medications.[7] [8] [9] [10] [11]

The FDA (US food and Drug Administration) has issued numerous warnings on their website[12] to advise consumers and physicians of the dangers that are posed by using some psychotropic medications. Numerous medical journals are publishing studies questioning the efficacy and or safety of some of these medications.[13] [14] [15] [16] [17]

The February 13, 2002 edition of the British Society Guardian published an article entitled "Psychiatrists Shift the Mood on Antidepressants." The Royal College of Psychiatrists, which represents about 10,000 psychiatrists, has taken a more cautious approach conceding that antidepressants such as Prozac may have only a 50% success rate in treating depression.[18]

Providing a question as to efficacy is the 1998 report published in the APA Journal entitled "Listening to Prozac but Hearing Placebo", the article details the meta-analysis of 19 drug studies. In short, the research showed that 75% of the "beneficial effect" of anti-depressant medication can be attributed to placebo effect. [19]

A July 5, 2002 study[20] also published in the APA Journal by Kirsch et al. analyzed all of the data submitted to the U.S. Food and Drug Administration (FDA) for approval of the six most widely prescribed antidepressants between 1987 and 1999. More than half of the 47 studies found that patients on antidepressants improved no more than those on placebos, Kirsch says. "They should have told the American public about this. The drugs have been touted as much more effective than they are." Celexa, Prozac, Paxil, Zoloft, Effexor and Serzone were part of this evaluation.[21] "They believe the difference between the patient's response to medication and response to placebo was small enough to be considered clinically meaningless." [22]

Research is showing that a significant number of serious side effects creating hospitalization admissions and even death (e.g. depression, cardiac arrest, serotonin syndrome, fatal poisoning etc.) are produced by the medications themselves. Many studies have supported these findings. [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52]

The New England Journal of Medicine, released on April 17, 2003, indicated that **1 in 4 patients receiving a medication prescription would be injured by that prescription.** The study presented by Gandhi et al.[53] revealed that the greatest source of injury was produced by the SSRI antidepressant type medications. "It is a problem that is common, in many cases the impact could be prevented or reduced, and it has a large impact on patients", said Tejal Gandhi an internist at Brigham and Women's Hospital in Boston, a Harvard University Facility.[54]

More than 200,000 Canadian school children take Ritalin (methylphenidate), yet the *Canadian Medical Association Journal* says the clinical trials of this drug have often been biased and poorly constructed. [12] [55] The Canadian article reviewed 62 randomized trials that involved a total of 2897 participants with a primary diagnosis of ADHD. The article stated, "However, these apparent beneficial effects are tempered by a strong indication of publication bias and the lack of robustness of the findings, especially those involving ADD features**. Methylphenidate also has an adverse event profile that requires consideration.**" In other words, these researchers believed that studies have tended to minimize the negative side effects of Ritalin.

Brain research carried out at John Hopkins University has shown that methamphetamine is toxic and damaging to both dopamine and serotonin brain neurons. In studies with laboratory rats, methamphetamine fed at 4 mg/day for only 3 days caused nerve fiber degeneration. Brain cells were permanently damaged by methamphetamine.[56] [57] Much more research is needed on the possible adverse effects of psychiatric medications on brain cells, especially in developing brains.

RELAPSE IN SPITE OF MEDICATION

Relapsing into a psychotic, depressive or bipolar episode while on medications is a common occurrence that leaves the patient crippled and despairing. Career, family, education etc. are put on hold while the patient works through the episode. Often, medication changes are initiated at this point, sometimes exacerbating the episode while the physicians attempt to bring a state of chemical balance into the patient's life. For the safety of the patient, hospitalization often occurs at this point, creating an even greater burden for the already overtaxed medical system. In spite of the best of medications, this revolving door phenomenon occurs all too often.

Gitlin et. al. reported in bipolar patients that despite continual medication maintenance treatment, data "indicated a 5-year risk of relapse into mania or depression of **73%**." Of those who relapsed, two-thirds had multiple relapses. Relapse could not be attributed to inadequate medication. Even for those who did not relapse, the presence of significant mood symptoms was observed. "Even aggressive pharmacological maintenance treatment does not prevent relatively poor outcome in a significant number of bipolar patients."[58]

Licht et al. reported significant relapse in 148 patients using only lithium as a mood stabilizer, thirty-two (21.6%) patients were readmitted within two years with a new affective disorder episode.[59]

In another relapse study, 15 patients with bipolar I disorder, who relapsed while on lithium despite positive initial response and adequate compliance, were treated by cognitive-behavioral methods in an open trial.[60] In follow-up ranging from 2-9 years, 5 of the 15 patients (33%) experienced a new affective episode.

A study involving two groups of patients taking either risperidone or haloperidol showed that the risk of relapse of schizophrenia was 34% for the former and 60% for the latter.[61] Many mentally disordered individuals travel a "revolving door". Their episodes of relapse can be devastating, destroying their hopes for wellness, as well as their careers and family stability.

Summary:
Psychiatric medications do not overcome the risk for relapse which is very high for both affective disorders and psychosis. [62] [63] [64] [65]

SIDE EFFECTS - THE UNTOLD DANGER

Table 2 Below shows the top ten most commonly prescribed psychiatric medications in the U.S.[66] for the year 2000. We will now review each one individually for side effects. The information in the following is somewhat limited. In other words the side effects presented by these medications are more extensive than indicated.

#	BRAND NAME	GENERIC NAME	MED. CLASS
1	Xanax	Alprazolam	Benzodiazapine
2	Zoloft	Sertraline	SSRI
3	Prozac	Fluoxetine	SSRI
4	Paxil	Paroxetine	SSRI
5	Ativan	Lorazepam	Benzodiazapine
6	Elavil	Amitriptyline	Antidepressant
7	Ambien	Zolpidem	Sleep Aid Hypnotic
8	Desyrel	Trazodone	Sleep Aid Hypnotic
9	Valium	Diazepam	Benzodiazapine
10	Klonopin	Clonazepam	Benzodiazapine

Benzodiazepine Class of Medications
1. Xanex (Alprazolam), 5. Ativan (Lorazepam), 9. Valium (Diazepam), 10. Klonopin (Clonazepam)

Benzodiazepine Addiction & Withdrawal:
In Canada the benzodiazepines are considered to be a controlled medication. The Canadian Compendium of Pharmaceuticals and Specialties (CPS) quotes the following side effects for the benzodiazepines:

"WARNINGS: Benzodiazepines are not recommended for use in patients with a major depressive disorder or psychosis in which anxiety is not a prominent feature. **PRECAUTIONS:** Benzodiazepines may cause psychologic or physical dependence… Abrupt (or gradual reduction) of benzodiazepines may lead to symptoms such as anxiety, insomnia, irritability, gastrointestinal discomfort, anorexia, diaphoresis, photophobia, or increased sensitivity to noise. More severe symptoms may occur such as confusion, depersonalization, myoclonus, delirium, psychosis,[67] [68] or seizures." [69]

Health Canada made the following statements in their report entitled "The Effects of Tranquillization: Benzodiazepine Use in Canada."[70]

- ✓ "The major indication of dependence is the development of withdrawal symptoms, which have been now clearly established at therapeutic dose levels." [71] [72] [73] [74] [75] [76] [77]
- ✓ "The high incidence of withdrawal symptoms suggests that a substantial minority of patients taking benzodiazepines chronically are pharmacologically dependent."[78]
- ✓ "One such carefully controlled study of withdrawal symptoms in patients who had been on ***low doses of benzodiazepines*** for a mean of 3.6 years, found between 27 and 45 percent evidencing clear withdrawal symptoms."[79]
- ✓ Babies have been born in an addicted state to mothers using benzodiazepines: "neonates born to drug-dependent women have shown withdrawal symptoms."

Addiction of unborn and newly born children is a major phenomenon. Medication withdrawal syndromes have been observed increasingly in children with mothers using psychotropic medications.[80] Research into babies suffering with Neonatal Withdrawal Syndrome report the following symptoms: continuous high-pitched cry, frantic sucking of fists, tremors, poor sucking response, sweating, and in some cases convulsions.[81] [82]

Cancer Risk from Benzodiazepine and Antidepressant Usage
Two studies have reported a positive association between antidepressant and benzodiazepine use and the development of cancer. Harlow and Cramer [83] carried out a case control study of ovarian cancer incidence and obtained an adjusted risk ratio of **2.1,** indicating that use of these medications for

more than 1-6 months resulted in more than doubling a woman's risk of ovarian cancer. Among women who first used these drugs before age 50 years the odds ratio was **3.5**. Among those who used them more than 10 years, the risk increased to **9.7**.

Dalton and colleagues[84] recently conducted a population-based study that followed for 7 years a total of 30,807 adult antidepressant users. They found an increased risk of non-Hodgkin's lymphoma among subjects who received greater than 5 prescriptions.

Indiscriminate and Irresponsible Prescribing of Benzodiazepines by Medical Practitioners

Treatment guidelines in the U.K. recommend the use of benzodiazepines for a maximum of 4 weeks. In Canada and the U.S. it is common practice to prescribe these medications for years.

Health Canada guidelines recommend prescribing only for short term use: "continuous use should not exceed two weeks".[85]

"The costs of continued use of benzodiazepines require careful consideration. The concern with payment must extend beyond the price of prescriptions to the total cost to the health care system. Inappropriate prescribing may well keep individuals visiting physicians…for considerably longer than necessary." [86] Many studies have supported this position. [87]

Summary

Benzodiazepines are medications that can be very dangerous when not used prudently. Cancer research shows that patients using benzodiazepines for over 10 years exhibit a 970% increase in risk of developing ovarian cancer. Addiction and withdrawal symptoms have been well established in scientific literature. Health Canada has issued warnings about prescribing of benzodiazepines in excess of two weeks. However, many physicians in North America prescribe them in an indiscriminate manner, as demonstrated by the fact that Xanex is the most frequently prescribed psychotropic medication.

SSRI Class of Medications

2. Zoloft (Sertraline), 3. Prozac (Fluoxetine), 4. Paxil (Paroxetine)

Cancer Risks Associated With Paxil Usage

The *American Journal of Epidemiology* published two studies in 2000 by Cotterchio and colleagues which demonstrated that Paxil presented a **720%** increase in risk of breast cancer in females. [14] [88] The Canadian Cancer Society website indicates that for heavy smokers there is a **400%** increase in risk for cancer. In other words, Paxil use creates a greater risk factor for breast cancer than heavy smoking. With over **3,000,000** Canadian prescriptions for Paxil in the year 2000 this is major cause for concern.[89]

SSRI's and Withdrawal Symptoms

On Februray 2, 2002 the British Medical Journal published an article entitled "Withdrawal from paroxetine can be severe, warns FDA". The article outlined in detail how paroxetine (Paxil) creates dependence and withdrawal in a significant percentage of patients. "This drug has been promoted as safe and easy to discontinue," said Charles Medawar, head of Social Audit. "The fact that it can cause intolerable withdrawal symptoms of this kind and lead to dependence is enormously important…" Dr. Peter Haddad, consultant psychiatrist for Salfords Mental Health Service NHS Trust, welcomed the FDA's safety warning. He said, "Withdrawal side effects from antidepressants are far more common than many people realize."[90]

The FDA issued a warning about Paxil on December 14, 2001. **"**During *Paxil* marketing, there have been spontaneous reports of similar adverse events… upon the discontinuation of *Paxil* (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. **Similar events have been reported for other selective serotonin reuptake inhibitors**." [91]

The above FDA statement describes some of

the symptoms of protracted withdrawal. In some cases these symptoms can persist for a number of years.

Studies involving other SSRI's including Luvox showed negative results in drug withdrawal.[92] A group of French researchers reported severe withdrawal syndromes in 6 patients prescribed Effexor (Venlafaxine).[93] There have been hundreds of studies published in the medical literature which demonstrate the significant symptoms that are produced when withdrawing from SSRI drug treatment. [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110] [111] [112] [113] [114] [115] [116] [117] [118] [119] [120] [121] [122] [123] [124] [125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141] [142] [143] [144] [145] [146] [147] [148] [149] [150]

ABC News reported on May 24, 2001 that "up to 85% of patients who take these kinds of drugs (SSRIs) may have some type of symptom when they stop, studies say. According to recent research in the *Journal of Clinical Psychiatry,* as many as 70% of General Practitioners and 30% of psychiatrists do not know about the side effects of ending serotonin boosting drugs. Getting off these drugs properly is an issue that is underappreciated," says Dr. Alexander Bodkin, director of the clinical psychopharmacology research program at Mclean Hospital. **"These drugs are being prescribed without the full knowledge of how they should be monitored."** [151]

As with the benzodiazepines, babies have been born in an addicted or toxic state to mothers using SSRIs. [152] [153] [154] [155] [156] [157]

Akathisia from SSRIs

Akathisia is a medication-induced disorder consisting of extreme restlessness, irritability and agitation.[158] [159] [160] [161] [162] It is often associated with the withdrawal symptoms of insomnia, headaches, nervousness, anxiety, anorexia, tremors, weight loss, nausea, diarrhea and can be coupled with **suicidal ideation, homicidal thoughts and or acts.**[163]

The number of people using psychotropic medication who suffer with Akathisia is significant. A study on Prozac reported in the *Journal of Clinical Psychiatry* estimated that the number of Prozac users who experience Akathisia is between 10 and 25%.[164] There are numerous studies relating psychotropic medication-induced Akathisia with suicidal, homicidal, and violent behavior.[165] [166] [167] [168] [169] [170] [171]As reported in a two-year study, Akathisia may create an inability to control impulses.

SSRIs and Suicide

Other researchers found that patients suffering Prozac-induced Akathisia became preoccupied with thoughts of suicide.[172] [173] [174] [175] [176] [177] Symptoms of agitation, panic, anxiety, mania and Akathisia can prompt suicidal or violent acts.[178] [179] [180] Akathisia and associated extreme acts of violence have been reported with other categories of psychiatric medication. For instance, Haldol-induced Akathisia was reported in three patients who attacked other people or committed murder.

Paxil (Seroxat) has been found to increase suicidal ideation and suicide in youth. **"**New expert advice recommends that the drug Seroxat (paroxetine) is not used to treat children and teenagers under the age of 18 years", said Professor Alasdair Breckenridge, Chairman of the U.K. Medicines and Healthcare Products Regulatory Agency. "It has become clear that the benefits of Seroxat in children for the treatment of depressive illness do not outweigh these risks." [181] The British government has now prohibited sales of Paxil (Seroxat) for youth under the age of 18.[182]

There have been a number of lawsuits involving medication and Akathisia. The following is an Associated Press release:

CHEYENNE, Wyo. (AP) June 6, 2001: *"The manufacturer of the nation's second-best-selling anti-depressant must pay $8 million to the relatives of a man who killed himself and three others after taking the drug Paxil, jurors said.*

Jurors in U.S. District Court considering the wrongful death civil suit returned a verdict against SmithKline Beecham today. They received the case Tuesday afternoon. Relatives of Donald Schell, 60, claim the man, originally from Gillette, Wyo., took two Paxil tablets

before shooting his wife, their daughter, his granddaughter and himself to death on Feb. 13, 1998."

Research published in the *American Journal of Psychiatry* supports the possibility that SSRI medications may induce suicidal ideation in some patients. The study, by Teicher and colleagues at Harvard Medical School, reported on six patients who were depressed but *not* suicidal before they started taking SSRI medication. Within a few weeks of taking the drug, the patients experienced "intense, violent suicidal preoccupation." [183]

Another important study involving children and adolescents and the use of Prozac demonstrated self destructive phenomena created by Akathisia.[184]

Psychiatric medications in other categories:

6. Amitriptyline (Elavil)

Amitriptyline is a tricyclic antidepressant with many side effects, as demonstrated by the following:

"Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Tricyclic antidepressant drugs, including amitriptyline HCl, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class. After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance." [185]

In a recently published study on "The effects of tricyclic antidepressants on breast cancer risk" published in the *British Journal of Cancer,* a number of the tricyclics were implicated in raising the risk of breast cancer. Amitriptyline was an exception, and was not shown to increase cancer risk rate, while some of the other TCA's (tricyclic antidepressants) did.[13] [84]

A number of studies have shown that tricyclic medications have induced manic episodes in patients suffering with various mental disorders. [186] [187] [188]

7. Ambien (Zolpidem)

Ambien is commonly used as a sleep aid. Like the other top ten medications, it has a number of negative side effects. The following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last Zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort.[189] [190] There have been adverse events reported such as delirium, nightmares and or mania being induced in patients using Zolpidem. Research is also showing that Zolpidem may create dependence in some patients.[191] [192] [193] [194]

8. Desyrel (Trazodone)

Trazodone is also used as a common sleep aid. Research has shown numerous negative events associated with Desyrel usage. [195] [196] [197] [198] [199] [200]

Summary

Hundreds of studies suggest that further research is needed on the safety of psychiatric medications. ADRs are a major cause of illness and death. **The top ten most prescribed psychotropic medications exhibit serious and dangerous side effects**. Addiction and withdrawal have become huge problems for many patients using psychotropic medications. The efficacy of these medications is also being questioned by many psychiatrists and especially by the patients using them.

FOOTNOTE REFERENCES:

[1] Lazarou J et al. (1998). Incidence of adverse drug reactions in hospitalized patients. *JAMA, 279,* 1200-5

[2] Johnson J, Bootman L (1995). Drug related morbidity and mortality, *Arch Intern Med 155*, 1949-1956

[3] Ernst F.R., Grizzle A.J., Drug Related Morbidity and Mortality: Updating the Cost-of-Illness Model, J Am Pharm Assoc. 2001;41:192-9

[4] Johnson J, Bootman L (1995). Drug related morbidity and mortality, *Arch Intern Med 155*, Page 1954 (Table 4)

[5] Kohn LT et al., To err is human: Building a safer health system. Washington D.C. Institute of Medicine 1999

[6] Leape L (2000). Institute of Medicine medical error figures are not exaggerated. *JAMA, 284,* 95-97

[7] Reuters: "Company Strengthens Warning on Schizophrenia Drug -- Clozaril", February 21, 2002.

[8] ABC News: "Antidepressants – Suicide Link: Harvard Psychiatrist calls for studies", May 15, 2001

[9] ABC News: "Falling Off Prozac" May 24, 2001.

[10] National Post: "Little Scientific Proof Ritalin Effective, Researchers Discover" Nov 27, 2001.

[11] The Globe and Mail: "Prozac May Trigger Suicide", April 14, 2001

[12] FDA WEBSITE
http://www.fda.gov/medwatch/safety.htm

[13] Sharpe CR et al. (2002). The effects of tricyclic antidepressants on breast cancer. *British Journal of Cancer*, *86*, 92-97

[14] Cotterchio M et al. (2000). Antidepressant medication use and breast cancer risk. *Am J Epidemiol*, *152,* 951-957

[15] Venning G (2000). Antidepressant drugs have previously been shown to be ineffective in mild depression, *Brit Med J*, *320*, 311

[16] Van Praag H (1996). Psychiatry and the march of folly? interview with D. Healy in *The Psychopharmacologists*, London: Chapman & Hall (Altman), 367.

[17] Moncrieff J, Are antidepressants overrated? A review of methodological problems in antidepressant trials. *J Nervous & Mental Disease*, 2001, 189, 288-295.

[18] Society Guardian February 13, 2002
http://society.guardian.co.uk/mentalhealth/story/0,8150,649503,00.html

[19] Kirsch I, et al., "Listening to Prozac but Hearing Placebo" APA, Prevention and Treatment, Vol 1,Article 0002a, June 26, 1998

[20] Kirsch I, et al., "The Emperor's New Drugs" APA Prevention and Treatment, Vol 5, Article 23, July 15, 2002

[21] USA Today July 7, 2002 – Study: Antidepressants Barely Better Than Placebo.

[22]APA Press Release July 5, 2002
http://www.apa.org/releases/antidepressants.html.

[23] Fluvoxamine (Faverin): Adverse reaction profile. *Current Problems in Pharmacovigilance*, No 22, May 1988, 1-2. www.socialaudit.org/REFS.html

[24] Palmer JL (2000). Postoperative delirium indicating an adverse drug interaction involving the SSRI, paroxetine, *J Psychopharmacol*, *14*, 186-188

[25] Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK (1998). Adverse drug reactions, *Brit Med J*, *316*, 1295-1298.

[26] Preda A. et al., Antidepressant – associated mania and psychosis resulting in psychiatric admissions. J Clin Psychiatry 2001 Jan;62(1):30-3

[27] Warren M. et al., Two case reports of trazodone – induced mania. Am J Psychiatry 1984 Sep;141(9): 1103-4

[28] Sandyk R, Hurwitz MD "Toxic irreversible encephalopathy induced by lithium carbonate and haloperidol. A report of 2 cases.

[29] Hoehn J. et al., "Sudden cardiac death with clozapine and sertraline combination". Ann Pharmacother 2001 Jul-Aug:35(7-8):862-6

[30]Steiner W. et al., Neuroleptic – induced supersensitivity psychosis in patients with bipolar affective disorder. Acta Psychiatr Scand 1990 May;81(5):437-40

[31] Go F.S., Malley E.E., et al., Manic Behaviors associated with fluoxetine in three 12 -18 year – olds with obsessive – compulsive disorder J Child Adolesc Psychopharmacol 1998;8(1):73-80

[32] Yuvarajan R., et al., Mania induced by lithium augmentation. A case report. Br. J Psychiatry 1988 Dec; 153:828-30

[33] Suraya Y., et al., Lithium neurotoxicity. Med J Malaysia 2001 Sep;56(3):378-81

[34] Howland R.H., Induction of mania with serotonin reuptake inhibitors. J Clin Psychopharmacol 1996 Dec;16(6):425-7

[35] Dorevitch A., et al., Fluvoxamine – associated manic behavior: a case series. Ann Pharacother 1993 Dec;27(12):1455-7

[36] Tueth M.J., Emergencies caused by side effects of psychiatric medications. Am J. Emerg Med. 1994 Mar;12(2):212-6

[37] Black DW, et al., Depersonalization syndrome induced by fluoxetine. Psychosomatics 1991 Fall;32(4):468-9

[38] Van Scheyen JD., et al., Clomipramine – induced mania in unipolar depression. Arch Gen Psychiatry 1979 May;36(5):560-5

[39] Reiss AL., et al., Carbamazepine – induced mania in two children: case report. J Clin Psychiatry 1984 Jun;45(6):272-4

[40] Hurowitz GI., et al., Antidepressant – induced rapid cycling: six case reports. J Clin Psychopharmacol 1993 Feb;13(1):52-6

[41] Berk M., et al., Antidepressant induced mania in obsessive compulsive disorder. Eur Neuropsychopharmacol 1996 Mar;6(1):9-11

[42] Henry C., Et al., Antidepressant – induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001 Apr;62(4):249-55

[43] Hall KL, et al., Neuroleptic malignant syndrome due to olanzapine. Psychopharmacol Bull. 2001 summer,35(3):49-54

[44] Berardi D., et al., Clinical risk factors for neuroleptic malignant syndrome. Hum Psychopharmacol. 2002 Mar;17(2):99-102

[45] Viejo LF., et al., Risk factors in neuroleptic malignant syndrome. A case-controlled study. Acta Psychiatr Scand. Jan;107(1):45-9

[46] Frey R., et al., Fatal poisonings with antidepressant drugs and neuroleptics. Analysis of a correlation with prescriptions in Vienna 1991-1997

[47] Fux M., Emergence of depressive symptoms during treatment for panic disorder with specific 5-hydroxytryptophan reuptake inhibitors. Acta Psychiatr Scand. 1993 Oct;88(4);235-7

[48] Aysegul Y., et al., Do Antidepressants Induce Rapid Cycling? A Gender-Specific Association, J Clin Psychiatry 2003;64:814-818

[49] Becker D., et al., Risperidone, but Not Olanzapine, Decreases Bone Mineral Density in Female Premenopausal Schizophrenia Patients. J Clin Psychiatry 2003;64:761-766

[50] Janssen Ortho Warning: TOPAMAX, Reports of Hyperthermia in patients treated with TOPAMAX.

[51] Lantz MS. Serotonin syndrome. A common but often unrecognized psychiatric condition. Geriatrics. 2001 Jan;56(1):52-3

[52] Azaz-Livshits T. Paroxetine associated hepatoxicity: a report of 3 cases and a review of the literature. Pharmacopsychiatry. 2002 May;35(3):112-5

[53]Gandhi T.K. et al., "Adverse Drug Events in Ambulatory Care" NEJM, Vol. 348:1556-1564, April 17, 2003 Number 16.

[54] Reuters: "Prescription Drug Side Effects Hit 1 in 4", April 18, 2003

[55] Schachter B et al. (2001). How efficacious and safe is short-acting methylphenidate for the treatment of Attention–Deficit Disorder in children and adolescents? *CMAJ*, *27*, 165.

[56] Ricaurte GA et al. (1984). Further evidence that amphetamines produce long lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. *Brain Res 303*, 359-64

[57] Ricaurte GA (1992). Neurotoxic amphetamine analogues: Effects in monkeys and applications for humans. *Ann NY Acad Sci, 648,* 371-82

[58] Gitlin MJ, Swendsen J, Heller TL, Hammen C (1995). Relapse and impairment in bipolar disorder. *Am J Psychiatry, 152,* 1635-40

[59] Licht RW, Vestergaard P, Rasmussen NA, Jepsen K, Brodersen A, Hansen PE (2001). A lithium clinic for bipolar patients: 2-year outcome of the first 148 patients. *Acta Psychiatr Scand, 104,* 387-90

[60] Fava GA, Bartolucci G, Rafanelli C, Mangelli L (2001). Cognitive-behavioral management of patients with bipolar disorder who relapsed while on lithium prophylaxis. *J Clin Psychiatry, 62,*556-9

[61] Csernansky JG, Mahmoud R, Brenner R (2002). A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med, 346,* 16-22

[62] Byrne SE, Rothschild AJ (1998). Loss of antidepressant efficacy during maintenance therapy: possible mechanisms and treatments. *J Clin Psychiatry 59*, 279-288.

[63] Tollefson GD (1993). Adverse drug reactions/interactions in maintenance therapy. *J Clin Psychiatry, 54* (8 Suppl), 48-58.

[64] Stewart JW, Quitkin FM, McGrath PJ, Amsterdam JM, Fava J, Fawcett F, Reimherr J, Rosenbaum C, Beasley, C, Roback, P (1998). Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo, *Arch Gen Psychiatry*, *55*, 334-443.

[65] Sharma V (2001). Loss of response to antidepressants and subsequent refractoriness: diagnostic issues in a retrospective case series, *J Affective Disorders*, *64*, 99-106

[66] Scott-Levine, Newton PA – Based on more than 2.04 billion prescriptions. Year 2000www.rxlist.com

[67] Arana G. et al., Alprazolam- induced mania: two clinical cases. Am J Psychiatry 1985 Mar;142(3):368-9

[68] Reddy J. et al., Alprazolam – Induced Hypomania. Aust N Z J Psychiatry. 1996 Aug;30(4):550-2

[69] Compendium of Pharmaceuticals and Specialties (CPS) Thirty-Fifth Edition (2000) Pages 187-188 Canadian Pharmacists Association.

[70] Health and Welfare Canada, The Effects of Tranquillization: Benzodiazepine Use In Canada, published by authority of The Minister of National Health and Welfare, 1982

[71] Preskorn SH & Denner LJ (1977). Benzodiazepines and withdrawal psychosis. *JAMA*, *237*, 36-38

[72] Covi L, Lipman RS, Pattison JH, Derogatis LR, and Uhlenluth E H (1973). Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatrica Scandinavia*, *49,* 51-64

[73] Pevnick J S et al. (1978). Abrupt withdrawal from therapeutically administered diazepam, *Archives of General Psychiatry*, *35*, 995-998

[74] Petursson H & Lader MH (1981). Withdrawal from long-term benzodiazepine treatment, *Br Med J, 28*, 643-645.

[75] Marks J. *The Benzodiazepines - use, overuse, misuse, abuse.* Lancaster UK: MTP Press, 1978.

[76] DTB (Anon), (1985). Some problems with benzodiazepines, *Drug & Ther Bull, 26*, 11-12.

[77] Benzodiazepine dependence syndromes and syndromes of withdrawal. In Hallstrom C (Ed): *Benzodiazepine Dependence* (Oxford University Press, 1993)

[78] Tyrer et al. (1981). Benzodiazepine withdrawal symptoms and propranolol, The Lancet, 520-522

[79] Greenblatt DJ et al. (1978). Dependence, tolerance, and addiction to benzodiazepines: Clinical and pharmacokinetic considerations. *Drug Metabolism Reviews*, *8,* 13-28

[80] Perault MC, Favreliere S, Minet P, Remblier C (2000). Benzodiazepines and pregnancy, *Therapie,* 55, 587-95

[81] Longo L.P., Johnson B, Addiction: Part 1. Benzodiazepines-Side Effects, Abuse Risk and Alternatives. American Family Physician. April 1, 2000

[82] Finnegan L., United Nations Report, Jan 1, 1979 "Pathophysiological and behavioural effects of the transplacenta neonates of narcotic dependent mothers"

[83] Harlow BL, Cramer DW (1995). Self reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancers: Evidence from two combined controlled studies (Massachusetts, United States). *Cancer Causes Control, 6*, 130-134

[84] Dalton et al. (2000). Antidepressant medications and risk for cancer. *Epidemiology 11*, 171-176

[85] Health and Welfare Canada, The Effects of Tranquillization: Benzodiazepine Use In Canada, published by authority of The Minister of National Health and Welfare, 1982 Page 49

[86]Health and Welfare Canada, The Effects of Tranquillization: Benzodiazepine Use In Canada, published by authority of The Minister of National Health and Welfare, 1982

[87] H Ashton, Benzodiazepines, "How They Work and How to Withdraw". University of Newcastle, Jan 2000

[88] Lawlor DA et al. (2000). Re: "antidepressant medication use and breast cancer risk". Am J Epidemiol 152: 1105.

[89]IMS Health Canada as reported in the National Post & Globe and Mail - March 29, 2001

[90] Tonks A (2002). Withdrawal from paroxetine can be severe, warns FDA. *BMJ 324*, 260

[91] FDA Website: www.fda.gov/medwatch/safety/2001/dec01.htm#paxil

[92] Hirose S (2001). Restlessness related to SSRI withdrawal, *Psychiatry Clin Neurosci 55,* :79-80

[93] Pinzani V et al. (2000). Venlafaxine withdrawal syndrome: report of six cases and review of the literature, *Rev Med Interne 21,* 282-4

[94] Agelink MW, Zitselsberger A, Kleiser E (1997). Withdrawal symptoms after discontinuation of venlafaxine, *Am J Psychiatry*, *154*, 1473-1474.

[95] Amsden GW, Georgian F (1996). Orthostatic hypotension induced by sertraline withdrawal, *Pharmacotherapy*, *16*, 684-686.

[96] Anderson IM, Tomenson BM (1995).Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic anti-depressants: a meta-analysis. *Brit Med J, 310*, 1433-8.

[97] Antonuccio DO, Danton WG, DeNelsky GY, Greenberg RP, Gordon JS (1999). Raising Questions about Antidepressants, *Psychotherapy and Psychosomatics*, *68*, 3-14.

[98] Bakker A (1999). Severe withdrawal symptoms with fever upon stopping paroxetine (letter, in Dutch), *Ned Tijdschr Geneeskd*, *143*, 1795, discussion 1795-6.

[99] DK Arya, Withdrawal after discontinuation of paroxetine (letter), *Aust NZ J Psychiatry*, October 1996, 30 (5), 702

[100] Baldessarini RJ, Viguera AC, Tondo L (1999). Discontinuing psychotropic agents (comment on Healy and Tranter, 1999) *J Psychopharmacol*, *13*, 292-293.

[101] Barr LC, Goodman WK, Price LH (1994). Physical symptoms associated with paroxetine discontinuation (letter). *Am J Psychiatry, 151*, 289.

[102] Belloeuf L, Le Jeunne C, Hugues,FC (2000). Paroxetine withdrawal syndrome [Article in French], *Ann Med Interne (Paris) 151* Suppl A,A52-3.

[103] Benazzi F (1996). Venlafaxine withdrawal symptoms, *Can J Psychiatry*, *41*, 487.

[104] Benazzi F (1998). SSRI discontinuation syndrome related to fluvoxamine, *J Psychiatry & Neuroscience*, *23*, 94

[105] Benazzi F (1998). Nefazodone withdrawal symptoms, *Can J Psychiatry*, *43,* 194-195

[106] Benazzi F. (1998). Sertraline discontinuation syndrome presenting with severe depression and compulsions, *Biol Psychiatry*, *43*, 929-930

[107] Black DW, Wesner R, Gabel J (1993). The abrupt discontinuation of fluvoxamine in patients with panic disorder. *J Clin Psychiatry, 54*, 146-9

[108] Black K, Shea C, Dursun S, Kutcher S (2000). Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria, *J Psychiatry Neuroscience*, *25*, 255-261.

[109] Bloch M, Stager SV, Braun AR, Rubinow DR (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. *Lancet, 346*, 57.

[110] Boyd IW (1998). Venlafaxine withdrawal reactions, *Med J Aust*, *169*, 91-92

[111] Bryois C, Rubin C, Zbinden JD, BaumannP (1998). [Withdrawal syndrome caused by selective serotonin reuptake inhibitors: apropos of a case]. In German. *Schweiz Rundsch Med Prax*, *87*, 345-348.

[112] Haddad P (1998). The SSRI discontinuation syndrome, *J Psychopharmacology*, *12*, 305-313.

[113] Haddad P, Anderson I (1999). Antidepressants aren't addictive: clinicians have depended on them for years (comment on Healy and Tranter, 1999). *J Psychopharmacol*, *13*, 291-298.

[114] Huffstutler SY (1998). Management of antidepressant withdrawal reactions, *J Am Acad Nurse Pract*, *10*, 161-165.

[115] Pacheco L, Malo P, Aragues E, Etxebeste M (1996). More cases of paroxetine withdrawal syndrome, *Brit J Psychiatry*, *169*, 384.

[116] Parker G, Blennerhassett J (1998). Withdrawal reactions associated with venlafaxine. *Aust N Z J Psychiatry, 32*, 291-4.

[117] Pollock BG (1998). Discontinuation symptoms and SSRIs (letter), *J Clin Psychiatry*, *59*, 535-537.

[118] A comparison of the post-marketing safety of four selective serotonin reuptake inhibitors including the investigation of symptoms occurring on withdrawal, *Br J Clin Pharmacol*, 1996, 42, 757-763.

[119] Pyke RE (1995). Paroxetine withdrawal syndrome. *Am J Psychiatry*, *152,*149-50.

[120] Reeves RR, Pinkofsky LR (1996). Lhermitte's Sign in paroxetine withdrawal, *J Clin Psychopharmacol*, *16*, 411-412.

[121] Nathan RG, Kinney JL (1985). Long-Term Dependence on Antidepressants (letter), *Am J Psychiatry*, *142*, 524

[122] Zajecka J, Tracy KA, Mitchell S (1997) Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review, *J Clin Psychiatry*, *58*, 291-297.

[123] Young A, Haddad P (2000). Discontinuation symptoms and psychotropic drugs (letter), *The Lancet*, *355*, 1184

[124] Wolfe RM (August 1997). Antidepressant withdrawal reactions, *American Family Physician*, *56* (2).

[125] Young AH, Currie A (1997). Physicians' knowledge of antidepressant withdrawal effects: a survey, *J Clin Psychiatry*, *58* (suppl 7), 28-30.

[126] Wincor MZ (1998). Withdrawal symptoms associated with abrupt discontinuation of SSRIs, *J Am Pharm Assoc (Wash)*, *38*, 500-501.

[127] Walker-Kinnear M, McNaughton S (1997). Paroxetine discontinuation syndrome in association with sertindole therapy, *Brit J Psychiatry*, *170*, 389.

[128] Wade GS (2000). Controlled withdrawal for psychotropic drugs, *Lancet*, *355,* 1822-1823.

[129] Vergouwen AC, Kuipers T (1999). Severe withdrawal symptoms with fever upon stopping paroxetine (letter, in Dutch), *Ned Tijdschr Geneeskd*, *143*, 1794-5, discussion 1795-6.

[130] Health Canada, Paxil Warning, July 15, 2003 http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/paxil_pa_e.html

[131] Benazzi F., Pyschotic Mania in Bipolar 2 - Depression Related to Sertraline Discontinuation. Canadian Psychiatric Association, August 2002,

[132] Szabadi E (1992). Fluvoxamine withdrawal syndrome. *Brit J Psychiatry, 160*, 283-284.

[133] Strickland GM, Hough DW (2000). Unilateral facial numbness and visual blurring associated with paroxetine discontinuation (letter), *J Clin Psychopharmacol*, *20*, 271-272

[134] BBC News – Anti Depressant Safety Reviewed. Jan 8, 2003. http://news.bbc.co.uk/1/hi/health/2635181.stm

[135] Stahl MM, Lindquist M, Pettersson M, Edwards IR, Sanderson JH, Taylor NF, Fletcher AP, Schou JS. Withdrawal reactions with selective serotonin reuptake inhibitors (SSRIs) as reported to the WHO system, *Eur J Clin Pharmacol*, *53*, 163-169

[136] BBC News Patients may sue over anti-depressant. http://news.bbc.co.uk/1/hi/health/2041430.stm

[137] Rosenstock HA (1996). Sertraline withdrawal in two brothers: a case report. *Int Clin Psychopharmacol, 11*, 58-9.

[138] Rosenbaum JF, Fava M, Hoog S L, Ascroft R C, Krebs W B (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: A randomised clinical trial, *Biol Psychiatry*, *44*, 77-87.

[139] Rojas-Fernandez C, Gordon J (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: putative mechanisms and prevention strategies (letter), *Can J Psychiatry*, *43*, 523-524.

[140] Menecier P, Menecier-Ossia L, Bern P (1997). Fluoxetine dependence and tolerance. Apropos of a case (English abstract, French text), *Encephale*, *23*, 400-401.

[141] Mathew T (Chair, ADRAC), SSRIs and withdrawal syndrome, Neonatal Disorders. *Australian Adverse Drug Reactions Bulletin*, 15, 1, November 1996, 2.

[142] Maixner SM, Greden JF (1998). Extended antidepressant maintenance and discontinuation syndromes. *Depress Anxiety*, *8* Suppl 1, 43-53

[143] BBC News Prozac may encourage suicide. May 22, 2003 http://news.bbc.co.uk/1/hi/health/758763.stm

[144] Louie AK, Lannon RA, Ajari L J (1994). Withdrawal reaction after sertraline discontinuation (letter). *Am J Psychiatry, 151*, 450-1.

[145] Macbeth R, Rajagopalan M (1998). Venlafaxine withdrawal syndrome, *Aust NZ J Med*, *28*, 218.

[146] Louie AK, et al., (1998) Venlafaxine withdrawal reactions. Am J Psychiatry, 151, 450-1

[147] BBC News Antidepressant can be addictive. http://news.bbc.co.uk/1/hi/programmes/panorama/2321545.stm

[148] Buckley NA Fatal toxicity of serotoninergic and

other antidepressant drugs: analysis of United Kingdom mortality data *BMJ* 2002;325:1332-1333 Dec 7, 2002

[149] Johnson H, Bouman WP, Lawton J (1998). Withdrawal reaction associated with venlafaxine, *Brit Med J*, *317*, 787.

[150] Lehrman N. The SSRI Conference in Philadelphia, Oct 24, 2003

[151] ABC News May 24, 2001 "Falling Off Prozac" http://abcnews.go.com/sections/living/DailyNews/ssri000524.html

[152] Yapp P, Ilett KF, Kristensen J H, Hackett LP, Paech MJ (2000). Drowsiness and poor feeding in breast-fed infant: association with nefazodone and its metabolites, *Ann Pharmacocother, 34*, 1269-1272

[153] Nijhuis IJ, Kok-Van Rooij GW, Bosschaart AN (2001). Withdrawal reactions of a premature neonate after maternal paroxetine (letter), *Arch Dis Child Fetal Neonatal Ed, 84,* F77-78

[154] Stiskal JA, Kulin N, Koren G, Ho T, Ito S (2001). Neonatal paroxetine withdrawal syndrome (short report of four cases), *Arch Dis Child Fetal Neonatal Ed*, *84*, F134-F135. See comment (and author's response) by Ibister et al. in *Arch Dis Child Fetal Ed*, 2001, Sept, 85(2), F147-148

[155] Spencer, MJ (1993). Fluoxetine Hydrochloride (Prozac) Toxicity in a Neonate. *Pediatrics,* 92, 721-2.

[156] Mohan CG, Moore JJ (2000). Fluoxetine toxicity in a preterm infant, *J Perinatol*, *20*, 445-446.

[157] Nordeng H., et al., Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. Acta Paediatr. 2001 Mar;90(3):288-91

[158] Bertolin G., et al., Akathisia due to risperidone withdrawal: two clinical cases. Actas Esp Psiquiatr 2002 May-Jun;30(3):195-7

[159] Van Harten PN. Drug-induced akathisia. Ned Geneeskd 2002 Jan 19;146(3):110-4

[160] Chong SA., et al., Clinical characteristics and associated factors in antipsychotic-induced akathisia of Asian patients with schizophrenia. Schizophr Res 2003 Jan 1;59(1):67-71

[161] Brune M, The incidence of akathisia in bipolar affective disorder treated with neuroleptics – a preliminary report. J Affect Disord 1999 May;53(2):175-7

[162] Lima AR., et al., Anticholinergics for neuroleptic – induced acute akakthisia. Cochrane database Syst Rev. 2002;(3):CD003727

[163] Kim JH., et al., Subjective emotional experience and cognitive impairment in drug-induced akathisia. Comp Psychiarty 2002 Nov-Dec; 43(6):456-62

[164] Lipinski JF, Mallya G, Zimmerman P, Pope HG (1989). Fluoxetine-induced akathisia: Clinical and theoretical implications. *Journal of Clinical Psychiatry*, *59*, 339-42.

[165] Fava M., et al., Suicidality and fluoxetine: is there a relationship? J Clin Psychiatry. 1991 Mar;52(3):108-11.

[166] Leong GB., et al., Neuroleptic – induced akathisia and violence: a review. J forensic Sci 2003 Jan; 48(1):187-9

[167] Teicher MH., et al., Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf. 1993 Mar;8(3):186-212

[168] Kasantikul D., Drug induced akathisia and suicidal tendencies in psychotic patients. J Med Assoc Thai. 1998 jul;81(7):551-4.

[169] Healy D., Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. Psychother Psychosom. 2003 Mar- apr;72(2):71- 9

[170] Anderson GM., et al., Serotonin and suicidality: the impact of fluoxetine administration. Acute neurobiological effects. Isr J Psychiatry Relat Sci. 1995;32(1):344-50

[171] Lancon C., et al., Fluoxetine, akathisia, and suicide. Encephale. 1997 May-June;23(3):218-23

[172] Hamilton MS, Opler LA (1992). Akathisia, suicidality, and fluoxetine. *Journal of Clinical Psychiatry*, *53,* 401-6

[173] Tueth M.J., Akathisia causing suicide attempts in patients taking fluoxetine (prozac) J Emerg Med. 1993 May-Jun;11(3):336-7

[174] Rothschild AJ., et al., Re-exposure to fluozetine after serious suicide attempts by three patients: the role of akathisia. J clin Psychiatry. 1991 Dec;52(12):491-3

[175] Cem Atbasoglu, et al., The relationship of akathisia with suicidality and depersonalization among patients with schizophrenia. J Neuropsychiatry clin Neurosci 2001 Summer; 13(3):336-41

[176] Tueth MJ., Revisiting fluoxetine (Prozac) and suicidal preoccupations. J. Emerg Med. 1994 Sep-Oct;12(5):685-7

[177] King RA., Serotonin and suicidality: the impact of acute fluoxetine administration: Serotonin and suicide. Isr J Psychiatry Relat Sci. 1994;31(4):271-9

[178] Drake RE, Ehrlich J (1985). Suicide attempts associated with akathisia, *American Journal of Psychiatry*, 499-501.

[179] Hindmarch I, Kimber S, Cockle SM (2000). Abrupt and brief discontinuation of antidepressant treatment: effects on cognitive function and psychomotor performance, *Int Clin Psychopharmacol, 15,* 305-18

[180] Zubenko G. et al., Antidepressant – related akathisia. J Clin Psychopharmacol 1987 Aug; 7(4):254-7

[181] U.K. Department of Health , June 10, 2003 http://www.info.doh.gov.uk/doh/intpress.nsf/page/2003-0223?OpenDocument

[182] Press Release June 10, 2003, Prime Ministers Office , #10 Downing Street, London, England

[183] Teicher MH, Glod C & Cole JO (1990). Emergence of intense suicidal preoccupation during fluoxetine treatment, *American Journal of Psychiatry*, *147*, 207-10.

[184] King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P & Scahill L (1991). Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment, *Journal of the American Academy of Child and Adolescent Psychiatry*, *30*, 179.

[185] www.rxlist.com Listed side effects.

[186] Wehr TA, Goodwin FK (1979). Rapid cycling in manic-depressives induced by tricyclic antidepressants, *Arch Gen Psychiatry, 36,* 555-9

[187] Nelson JC, et al (1979). Exacerbation of psychosis by tricyclic antidepressants in delusional depression., *Am J Psychiatry, 136,* 574-6

[188] Zis AP et al. (1979). Tricyclic-induced mania and MHPG excretion. *Psychiatry Res*, *1,* 93-9

[189] www.rxlist.com Listed side effects

[190] Huang CL., et al., Zolpidem-induced distortion in visual perception. Ann Pharmacother, 37(5):683-6 2003

[191] Galder R., et al., Zolpidem: the risk of tolerance and dependence according to case reports, systematic studies and recent molecularbiological data. Fortschr Neurol Psychiatr, 69(12):592-6 2001

[192] Aragona M., Abuse, dependence, and epileptic seizures after Zolpidem withdrawal, a review and case report. Clin Neuropharmacol, 23(5):281-3, 2003

[193] Vartzopoulos D. Dependence on Zolpidem in high dose. Int Clin Psychopharmacol, 15(3): 181-2 2000

[194] Freudenreich O., Zolpidem-related delirium: a case report. J Clin Psychiary, 61(6):449-50 2000

[195] Lennkh C et al. (1998). Occurrence of trazodone – induced delirium. *Int clin Psychopharmacol, 13,* 225-8

[196] Jabeen S (1991). Trazodone – induced transient hypomanic symptoms and their management. *Br J Psychiatry, 158*, 275-8

[197] Knobler HY et al. (1986). Trazadone-induced mania. *Br J Psychiatry, 149*, 787-9

[198] Pae CU., et al., Association of lose dose trazodone treatment with aggravated angle glaucoma. Psychiatry Clin Neurosci, 57(1): 127-8 2003

[199] Rettman KS., et al., Hepatoxicity after short-term trazodone therapy. Ann Pharmacother, 35(12): 1559-61 2002

[200] Patterson DE., et al., Speech dysfunction due to trazodone – fluoxetine combination in traumatic brain injury. Taylor and Francis Health Sciences Vol 11, Number 4/ Apr 1, 1997

