

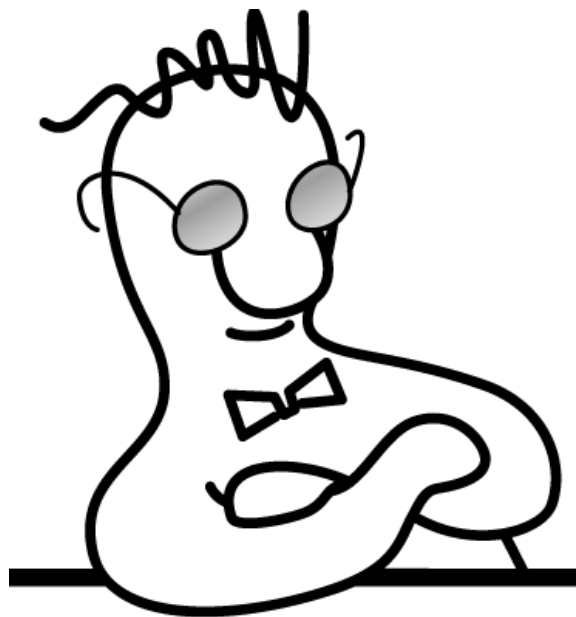


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The effectiveness of clozapine

Two recent studies have investigated further this major question.

Rosenheck et al. conducted a one-year study at 15 US Veteran Affairs medical centres from March 1993 to April 1995.¹ The patients had:

- DSM-III-R schizophrenia;
- serious social dysfunction (not defined) for the previous two years;
- severe symptoms (indicated by scores on the Brief Psychiatric Rating Scale and the Clinical Global Impressions Scale);
- high level of use of inpatient services (30 to 364 days of hospitalisation for schizophrenia in the previous year); and
- refractoriness (defined as persisting psychotic symptoms despite adequate trials of two or more antipsychotic drugs at 1000 mg chlorpromazine equivalents unless limited by adverse effects).

Treatments comprised clozapine 100 to 900 mg/d (n = 205) or haloperidol 5 to 30 mg/d (n = 218). Doses were adjusted according to need but from among 12 fixed dosage levels. Haloperidol patients received benztrapine 2 to 10 mg/d and clozapine patients a matching benztrapine placebo. A predefined program of psychotherapeutic and rehabilitative treatment was offered to the patients.

The most impressive result was that more clozapine patients continued the randomised, blinded treatment for the entire year - 117 (57%) clozapine patients versus 61 (28%) haloperidol patients, $p < 0.001$. Most haloperidol patients stopped because of lack of efficacy or worsening of symptoms (51% vs. 15%, $p < 0.001$). The major reasons for clozapine patients stopping the trial were side effects (30% vs. 17%) and what the investigators called non-drug-related reasons, such as not wanting to continue the trial, (55% vs. 32%).

This was an excellent result for clozapine but, as raised before (*Drug Wise 1997; 21: 40*), haloperidol is not a good comparator because it does not benefit chronically hospitalised refractory schizophrenic patients — clozapine will always look good against haloperidol. After all, how good is a reference drug, haloperidol, that fails in more than 70% of patients in one year when the treated condition needs therapy for years not 12 months. Can any drug be called a reference drug if it fails more often than it works? It would be refreshing to see clozapine compared with thioridazine, for example, for a change. The rest of the re-

sults must be seen in this dim light.

For example, symptom levels were only slightly lower on clozapine — 79.1 vs. 83.6 on the Positive and Negative Syndrome Scale of Schizophrenia ($p = 0.02$). Two questions arise:

1. Is this a clinically significant difference?
2. Even though the difference is minute, would it exist at all if the raters could not distinguish readily between clozapine and haloperidol patients because of their different side effects (i.e. the trial was not really blind)?

I would suggest that the answer to both questions is a resounding no.

Although differences were claimed on the basis of statistical significance there were no clinical differences in either positive symptoms (mean score on clozapine 19.5 vs. 21.2 on haloperidol, $p = 0.04$) or, most surprisingly, on negative symptoms (20.9 vs. 21.2, $p = 0.02$). These are remarkable findings for a drug that is supposed to be effective in treatment-resistant patients.

The symptom results also showed that there were 163 clozapine patients at 12 months (i.e. 79.5% of those that started the trial) and 159 haloperidol patients (72.9%) which makes the claim, above, that more clozapine patients could continue treatment for the entire year look odd. It is explained by digging further and discovering that patients who stopped haloperidol were continued on other antipsychotics and included in the results, above, on symptoms. The patients who crossed over to another drug and completed one year of therapy differed (and then only slightly) in only one aspect from clozapine patients — quality of life. That is, there was no difference in positive or negative symptoms between patients who completed one year so it is finally there in black and white — it's not clozapine that makes more people better, it's staying on treatment. Therefore one could assume, until this is tested, that reducing extrapyramidal side effects (virtually the only adverse effect that haloperidol has) makes people better and any drug that does that will suffice. This seems to be exactly what every study is currently showing.

The authors also stated that significantly more clozapine patients had a clinically important improvement in symptoms (defined as a 20% or greater reduction in symptoms) but buried the data supporting this assertion in their discussion. Easy to see why when the results are dragged out of the text — 24% of clozapine patients had clinical improvement after 6 weeks (vs. 13% haloperidol patients) but after one year 37% of clozapine patients had clinical improvement as did 32% of haloperidol patients. That is, the much trumpeted gain occurs early; dare I suggest when the reduced extrapyramidal effects of clozapine are being experienced by the patient and seen by the rater (e.g. less akathisia

is seen as less psychotic agitation). And the argument to continue clozapine for 9 months or more because of supposed late gains looks a bit forced on these data.

Quality of life was slightly better on clozapine (clozapine 44.4 vs. haloperidol 40.9) but there was no difference in either improvement over time or clinically significant improvement (20% or more) in quality of life.

As would be hoped and expected clozapine patients benefitted from greater reductions in tardive dyskinesia, akathisia, and extrapyramidal symptoms.

On the bright side, clozapine patients had 24.3 fewer days in hospital (143.8 vs. 168.1, $p = 0.03$). This was offset by:

- more units of outpatient service (133.6 vs. 97.9, $p = 0.03$),
- more expensive outpatient service (\$US8,473 vs. \$US3,474 per capita, $p < 0.001$), and
- higher cost of drugs (\$US3,199 vs. \$US367).

However, the reduced number of days in hospital made clozapine 4% cheaper overall (\$US57,785 vs. \$US60,226 in total per capita health care). That is, clozapine is slightly cheaper in a country with the highest hospital costs in the world — is it cheaper anywhere else?

Three clozapine patients developed agranulocytosis and all recovered fully on stopping the drug.

The authors concluded that “among patients with refractory schizophrenia and high levels of hospital use, clozapine was somewhat more effective than standard treatments, had fewer side effects, and did not increase the total cost of care.” Reasonable conclusions given the data but one can imagine a vigorous correspondence between the authors and the article's referees over the inclusion of the qualifier ‘somewhat’. Usually papers that require a “somewhat more effective” do not get published in *The New England Journal of Medicine* which rejects thousands of papers a year. Did the editors publish the paper because it shows clozapine's superiority or merely clozapine's rough equivalence? Is this the first nail in the coffin for clozapine?

The second nail was struck a little earlier, in late 1996, but was less noticeable as it was published in a less prominent journal. Essock and colleagues conducted a two-year study of clozapine's effectiveness in public sector hospitals (US).² They found that clozapine was effective but did not produce the dramatic improvements in symptomatology or hospital utilisation previously reported.

In 227 clozapine patients followed for 2 years (open-label study) and compared with patients receiving usual care there were significantly greater reductions in side effects, disruptiveness, and hospitalisation but clozapine was no more effective in reducing symp-

toms or improving quality of life. The groups did not differ in likelihood of being discharged; however, once discharged clozapine patients were less likely to be readmitted.

As Rosenheck et al. observed, the patients studied by Essock et al. were not as ill (mean BPRS score of 43) as those in Rosenheck et al.'s study (mean BPRS = 52) or in Kane et al.'s landmark study in 1988 (mean BPRS = 61).³ Rosenheck et al. therefore concluded that this suggests that the benefit of clozapine may be less strong in patients with less severe symptoms. They could have instead concluded that higher scores in any measure always allow a stronger possibility that a difference can be found simply because there is more potential for a fall to be larger and thus statistically significant.

These two studies show, in my view, that clozapine is one choice among treatments but that the first aim should be to minimise the extrapyramidal side effects of antipsychotic drug treatment generally and that this could be achieved with any low-potency typical antipsychotic or some of the newer so-called atypical antipsychotics whether they are low or high potency drugs. As Sir William Osler (1849-1919) said many years ago, "One should treat as many patients as possible with a new drug while it still has the power to heal!"

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Poppy tea and the Baker's first seizure

In 1992 and 1993 there were reports in the *Pharmabulletin* about poppy seeds being used as an opioid substitute.^{1,2,3,4} In Melbourne, King and associates have now reported poppy seeds as an occupational hazard.⁵

A 26-year-old baker had his first tonic-clonic seizure and was delirious and terrified afterwards, struggling against hallucinatory figures. He was driven to hospital by ambulance but his delirium had resolved when he arrived. His post-ictal state suggested a toxic encephalopathy but he denied taking drugs. In the ensuing week his business partner advised the authors that extra poppy seeds had been ordered for the bakery, up to 25 kg per week whereas only 3 kg were required.

Fortunately, a blood sample taken on the day of the seizure was stored in the laboratory. It had a very high concentration of morphine, nearly 3 mg/L. By comparison, the mean concentration of morphine in heroin addicts who die of overdose in Victoria is 0.6 mg/L, range 0.1-3.0 mg/L. Heroin use was excluded by the absence of its distinguishing metabolite 6-acetylmorphine.

He admitted drinking poppy tea at night in the bakery and of learning the practice from other bakers during his apprenticeship. He had been addicted to heroin and participated in a methadone program but several months after leaving the program he began using poppy tea (but not heroin) and his consumption and tolerance escalated steadily over the next year. He had withdrawal symptoms if he abstained for more than a day.

A sample of the tea he prepared had a morphine concentration of 0.14 mg/mL (140 mg/L) and when he had the seizure he was drinking up to 2 L of tea each day made from 4 kg of seeds.

He started on MS-Contin (slow-release morphine) 60 mg twice daily and at his last review was taking 20 mg twice daily without further seizures. He denied using poppy tea and his blood morphine concentration was down to 0.1 mg/L. How long before poppy seed is restricted in the baking industry?

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Ecstasy 1998

It is 10 years since we first noted the re-emergence of ecstasy when it was involved with five accidental deaths¹ and nearly as long since the first review of the drug was published after a spate of inquiries regarding its use in Melbourne.² Over the years adverse effects have emerged — neurotoxicity,³ toxicity due to fulminant hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, and liver failure including deaths after its use at dance or 'rave' parties.⁴ Various psychiatric side effects (paranoid psychosis, depression), the possible involvement of the serotonin syndrome in ecstasy-induced hyperthermia and the use of dantrolene in that syndrome were also reported.⁴ After a lull over the last few years in this publication it seems appropriate to now update ecstasy. There is a brief summary of this article (p. 5) for those who want the essentials.

Another amphetamine analogue — paramethoxyamphetamine (PMA) — was involved in several 'ecstasy' deaths in 1995-96. In most of those cases the users thought they were taking ecstasy but PMA was present as a contaminant. It appears there were 12 deaths in 1995-96 in Australia with at least six of them involving PMA, either alone or combined with MDMA.

Although 12 deaths are disturbing it is a smaller problem than heroin-related deaths (e.g. there were 152 heroin-related deaths in NSW alone in 1992). However, MDMA-related deaths are unpredictable — other people have taken similar amounts from the same source as overdose victims with only minor toxic effects. This has led to investigation of genetic variations in drug metabolism (see below).

Although animal studies have suggested that environmental temperature may be a critical determinant of susceptibility (and thus cooling in dance venues is important) an Australian case has suggested another factor.⁵ Parr and associates reported a 15-year-old girl who collapsed with respiratory arrest after taking ecstasy at a dance party. She presented to hospital with hyponatraemia and cerebral oedema and later died. Parr et al. postulated that a large water intake (as previously advised by various health authorities to counteract ecstasy's hyperthermic effects) contributed to the hyponatraemia.

Parr et al. noted 5 other reports in the international literature of hyponatraemia associated with ecstasy and that hyponatraemia creates a diagnostic dilemma as its signs may be indistinguishable from those of MDMA intoxication.⁶ An Australian guideline was being prepared in early 1997, and may now be available, to advise on environment (e.g. suitable "cooling-off" areas), fluid intake, the danger of combining ec-

stasy with other illicit drugs, and the early warning signs of toxicity which have been ignored in several reported cases.⁵

As noted above, dantrolene has been used successfully to treat ecstasy intoxication but this was criticised by Dowsett⁷ on the following grounds:

- MDMA-hyperthermia is probably a central effect and there is no evidence that dantrolene's effect on skeletal muscle would reverse that effect.
- One reason proposed for dantrolene's use in ecstasy-induced hyperthermia is dantrolene's 'success' in neuroleptic malignant syndrome (NMS) but a review of 202 cases of NMS found that any decline in mortality was independent of treatment with dantrolene.⁸
- Anecdotal reports of dantrolene in ecstasy-induced hyperthermia showed mixed results including one negative report in 6 cases.⁹

Denborough and Hopkinson then showed that ecstasy elevated calcium concentrations in human muscle cells. This implied that ecstasy-induced hyperthermia has a similar pathogenesis to malignant hyperthermia (MH) associated with anaesthetics. They further suggested that the inherited muscle cell disorder that predisposes to MH may also predispose to ecstasy-induced hyperthermia and thus that dantrolene could be an effective treatment.¹⁰

In response to three of the articles above,⁵⁻⁷ Gillman argued that ecstasy produces its toxicity via elevation of intra-synaptic serotonin (5-HT) concentration and that ecstasy intoxication produces serotonin syndrome (SS) and that hyperpyrexia is just one component of it. He noted that ecstasy produces a massive release of 5-HT from pre-synaptic terminals followed by depletion of brain serotonin — total brain serotonin is depleted by about 80% within four hours of a single injection of MDMA (in animal studies). Gillman therefore argued that:

- Dantrolene would not treat the hyperactivity or delayed neurotoxicity components of ecstasy-induced toxicity.
- Dantrolene may not be effective in SS.
- Conservative measures for the treatment of hyperpyrexia may be sufficient, but if they are not, then 5-HT receptor antagonists cyproheptadine and chlorpromazine are more appropriate than dantrolene.¹¹

However, clinicians have continued to use dantrolene as shown by the case of a young male who survived hyperpyrexia (42.9 °C) following MDMA ingestion. He developed convulsions, rhabdomyolysis, metabolic acidosis, and respiratory failure. This was successfully managed by assisted ventilation, aggressive fluid therapy, and the early administration of dantrolene, in addition to cooling measures. This was the first report of a survivor with such a severe hyperpyrexia.¹²

Another unusual report concerned a young woman who had taken ecstasy and was found to have a spontaneous pneumomediastinum (the presence of air or gas in the mediastinal tissues, usually found in infants and may lead to pneumothorax or pneumopericardium). The authors also discussed the association of spontaneous pneumomediastinum with drug abuse in general.¹³

As noted in the introductory paragraph, ecstasy has been shown to produce a long lasting neurotoxic degeneration of 5-HT neurones in several regions of the brain in several species. Colado and colleagues have now investigated whether this degeneration is likely to be the result of free radical-induced damage.

Their data indicated that a major mechanism by which MDMA induces damage to 5-HT neurones in rat brain was by increasing the formation of free radicals. In contrast, fenfluramine induced damage by another mechanism not involving free radicals. They therefore said you cannot argue that MDMA will not be neurotoxic in humans just because fenfluramine appears safe at clinical doses.¹⁴

The same team also investigated whether children borne to mothers taking ecstasy could have neurotoxic damage. Or at least that is what their title suggested — they actually studied rat brains which are remarkably uninformative about human pregnancies and brains. Nevertheless their data were optimistic as they showed that exposure to MDMA *in utero* during the maturation phase did not damage 5-HT nerve terminals in the foetal rat brain but did damage them in the brains of the (rat) mothers. They suggested that this may be due to MDMA being metabolised to free radical producing entities in the adult brain but not in the immature brain or, alternatively, to more effective or more active free radical scavenging mechanisms in the immature brain.¹⁵

Simantov and Tauber showed that MDMA was cytotoxic to human serotonergic JAR cells. MDMA altered the cell cycle, increased G2/M phase arrest, and induced DNA fragmentation in a cycloheximide-sensitive way. This apoptosis was not observed in nonserotonergic human NMB cells. [Ed. — I don't know what it means either but I thought someone might!].¹⁶

Neurotoxicity continued to be a concern when Cohen and Cocores reported an individual who developed perpetual neuropsychiatric symptomatology after having consumed MDMA. The case indicated that MDMA may induce long lasting effects, even after one exposure. They also reviewed the recurring side-effects associated with MDMA consumption and developed a table to depict the deleterious reactions that have occurred following MDMA ingestion.¹⁷

Some of ecstasy's effects might be mediated by

dopamine. As described above, MDMA is a potent releaser of 5-HT (by acting as a substrate at the 5-HT transporter) and causes toxicity to 5-HT neurones after repeated exposure. MDMA also releases dopamine (DA), although with less potency.¹⁸

Although a number of complications associated with MDMA have been reported, there is little information about hepatotoxicity as a result of MDMA ingestion. Brauer and associates reported the case of an 18-year-old female patient who regularly used ecstasy on weekends over a 2-month period. Within 2 days after taking some at a party, she was admitted to the hospital because of lethargy, vomiting, abdominal pain, stool discolouration, icterus, and darkened urine. On day 7 she developed fulminant hepatic failure with reduced hepatic coagulation factors and grade IV encephalopathy. Orthotopic liver transplantation was carried out 10 days after the ingestion. The patient made a full recovery within 72 hours and was released from the hospital 6 weeks later. Histopathological examination of the removed liver revealed a nutritive-toxic liver necrosis. The case demonstrated that the ingestion of ecstasy, even on an infrequent basis, could lead to acute fulminant liver necrosis, and that this life-threatening complication can be treated successfully by liver transplantation.¹⁹

Amidst all of these, mainly physical, adverse effects was an intriguing report of mid-week depression after weekend ecstasy use. Twelve MDMA users were compared with 12 participants who reported having consumed only alcohol, on the relevant night (day 1). Both groups were then re-assessed the following day (day 2) and again mid-week (day 5). Curran and Travill found that the acute effects of MDMA were much the same as previous findings but things were different later in the week. MDMA users had elevated mood on day 1 but significantly low mood on day 5, at which point some participants scored within the range for clinical depression. In contrast, the alcohol group showed less pronounced changes, which followed a U-shaped curve over days with the lowest point being day 2. The MDMA group also showed significant impairments on an attentional/working memory task, compared with alcohol users. They concluded that weekend use of MDMA may lead to depressed mood mid-week. Possible mechanisms were temporary depletion of serotonin, serotonergic neurotoxicity and psychological aspects of mood change.²⁰

Summary

While neurotoxicity has been a recurring theme, reports of other toxicities have emerged as follows:

- another amphetamine analogue has appeared —

paramethoxyamphetamine (PMA) — and it was involved in several ecstasy deaths;

- dantrolene's use in ecstasy-induced hyperthermia provoked some controversy with a persuasive case made that ecstasy intoxication produces serotonin syndrome and that hyperpyrexia is just one component of it. Thus conservative treatment of hyperpyrexia may be sufficient; but if it is not, then 5-HT receptor antagonists like cyproheptadine and chlorpromazine are more appropriate than dantrolene;
- long lasting neurotoxic degeneration of 5-HT neurones is likely to result from free radical-induced damage and one case was reported of perpetual neuropsychiatric symptomatology after just one exposure to MDMA;
- some of ecstasy's effects might be mediated by dopamine partially through a 5-HT-mediated release of dopamine;
- hyponatraemia and cerebral oedema leading to death was reported, as was spontaneous pneumomediastinum, and acute fulminant liver necrosis (treated successfully by liver transplantation); and lastly
- a week-end 'high' with ecstasy was followed by a mid-week low.

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Correspondence

Nefazodone and breast cancer

Sir,—I have had an enquiry from a patient saying that she has read in a journal called 'Depression Awareness Journal' that antidepressants affecting 5-HT receptors should not be taken by patients with breast cancer.

This patient is taking nefazodone 500 mg/d and has recently had breast cancer removed. I cannot see any reference to this in the advisory pamphlet enclosed with nefazodone. Have you come across this complication?

Dr Ross Martin

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Reply

The current Product Information for nefazodone (Serzone) has a brief mention of this problem. Essentially, nefazodone increases prolactin serum levels and about one-third of human breast cancers are prolactin-dependent *in vitro*, i.e. prolactin encourages the growth of cultured breast cancer cells. This raises a few questions.

Does nefazodone increase prolactin levels?

It does and it doesn't. In male volunteers, prolactin levels were increased to twice baseline levels after acute administration of nefazodone but all values still remained within the normal range of 2–15 nanogram/mL. As well, the prolactin levels returned to baseline and, for example, there was no increase seen after 7-day dosing.

This was described by Walsh and Cowen (probably the same source as used for the product information, i.e. reported once only, not twice) and they proposed that acute treatment with nefazodone increased prolactin concentrations via metabolism to metachlorophenylpiperazine, a 5-HT₁ receptor agonist. They suggested that the attenuation of these effects after subacute treatment could be due to an adaptive down-regulation of 5-HT₁ receptors or to direct blockade of 5-HT₁ receptors by nefazodone and its metabolite hydroxynefazodone (OH-nefazodone). The concentrations in plasma of OH-nefazodone increased substantially during the 7-day treatment period.

But what about women? Prolactin levels were not determined in women in the pre-marketing clinical studies but there were no clinical signs of hyperprolactinaemia (e.g. amenorrhoea, galactorrhoea, abnormal menstrual cycle length) in the 446 women

who took nefazodone for more than 60 days in clinical studies. The product information suggests weighing the possible risk of hyperprolactinaemia against the benefits of therapy in women with existing breast cancer or with a history of the disease (as in this patient).

Does hyperprolactinaemia occur with other antidepressants?

Yes. It has been reported with SSRIs, clomipramine, and nortriptyline.

Spigset and Mjorndal found that 2 subjects, out of 8 healthy subjects, had substantial increases in serum prolactin levels (up to 35 nanogram/mL) during fluvoxamine treatment. They found some evidence that the increase in those 2 subjects was mediated by 5-HT₂ receptors.

Meltzer and colleagues found that chronic treatment with fluoxetine increased plasma prolactin but tricyclic antidepressants did not. The effect was observed in patients with major depression or obsessive compulsive disorder and also occurred when the patients were given L-5-hydroxytryptophan 200 mg. L-5-hydroxytryptophan is a precursor of serotonin (5-hydroxytryptamine) and it produced increases in plasma prolactin in the patients whether they took the antidepressants or not. That is, anything that increases 5-HT might increase prolactin rather than it being a specific receptor effect. The L-5-hydroxytryptophan-induced prolactin response was significantly higher in fluoxetine-treated than in tricyclic-treated or unmedicated major depressed patients.

Clomipramine and nortriptyline have been reported to stimulate prolactin release but amitriptyline, desipramine, and imipramine have been reported to be without effect.

Do increased prolactin levels really increase the risk of breast cancer?

Women with breast cancer were twice as likely to have prolactin levels higher than the median in plasma samples taken at least 3 months after breast cancer surgery. This has been phrased as 'prolactin levels over the median doubles the risk of breast cancer'.⁶ But that surely cannot be correct if the plasma samples are taken after the breast cancer is diagnosed, and removed, because it assumes that a high prolactin level after the event corresponds to a high level before breast cancer. But there is a high degree of suspicion that high prolactin levels should be avoided.

What are the treatment choices in this situation?

Thinking of legal complications, the cautious stance would be to change the patient to one of the three antidepressants that did not increase prolactin levels — amitriptyline, desipramine, or imipramine. And then

monitor plasma prolactin because one report that those drugs did not increase prolactin does not preclude them from increasing prolactin levels in another instance. However, a patient may have a history of not responding to any of those 3 drugs or have a history of pronounced adverse effects with them.

Secondly, one could seek the opinion of a specialist in breast cancer. But then that person's focus is on the breast cancer, not the mental disorder being treated, and one could hardly be surprised if the easy answer is to avoid any drug that has any evidence of increasing prolactin levels. It is rather like the easy response is always to avoid any drug use in the first trimester of pregnancy but that it not always in the patient's best interest.

Thirdly, the patient could be continued on nefazodone, especially if the disorder was severe or the patient suicidal and the response to nefazodone was marked. If this choice was considered it may be reassuring to know that antipsychotic drugs have had a similar concern about breast cancer for at least 20 years because they regularly produce hyperprolactin-aemia.⁷ Despite this concern for many years there is still no evidence that antipsychotic drug treatment (which is typically used for even longer periods than antidepressants) alters the risk of breast cancer.⁸

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Do SSRIs interact with sympathomimetics?

Jenny Gowan alerted me that *Drug Interaction Facts*, the well known text on interactions, has recently (July 1997) rated this combination as having major severity.

The single case concerned a 22-year-old woman who stopped fluoxetine (20 mg/d for 3 months) and then 8 days later took a single 30 mg tablet of the appetite suppressant phentermine (Duromine). Within several hours she complained of jitteriness, racing thoughts, stomach cramps, dry eyes, palpitations, and tremors. When she sat she rhythmically jiggled her feet and repeatedly sprang to her feet to pace. A single lorazepam 2.5 mg tablet resolved these symptoms.¹

The interaction report warned that the combination may increase sensitivity to sympathomimetics and increase the risk of serotonin syndrome (SS).

This warning, at the highest level of severity, seems a little excessive for a single case report given that SSRIs commonly produce akathisia (which seems a more accurate description) and mania (the racing thoughts) all by themselves.

Secondly, *Drug Interaction Facts* grouped fenfluramine and dexfenfluramine with 10 amphetamine analogues which appears to me to confuse the issue. While fenfluramine derivatives might sensibly be avoided during SSRI treatment because of a theoretical risk of SS, it would be surprising if amphetamine analogues increased the risk of SS (if more reports emerge we might conclude that). And once the term sympathomimetics is used there will soon be people telling patients they can't take nasal decongestants like Sudafed with SSRIs. If every adverse drug reaction during SSRI treatment and lasting half a day is going to be called SS then there will be no end of reports.

In addition, similar symptoms have been reported during SSRI withdrawal without any sympathomimetic being added (*Drug Wise* 1995, 19: 39-40). One swallow does not a summer make.

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