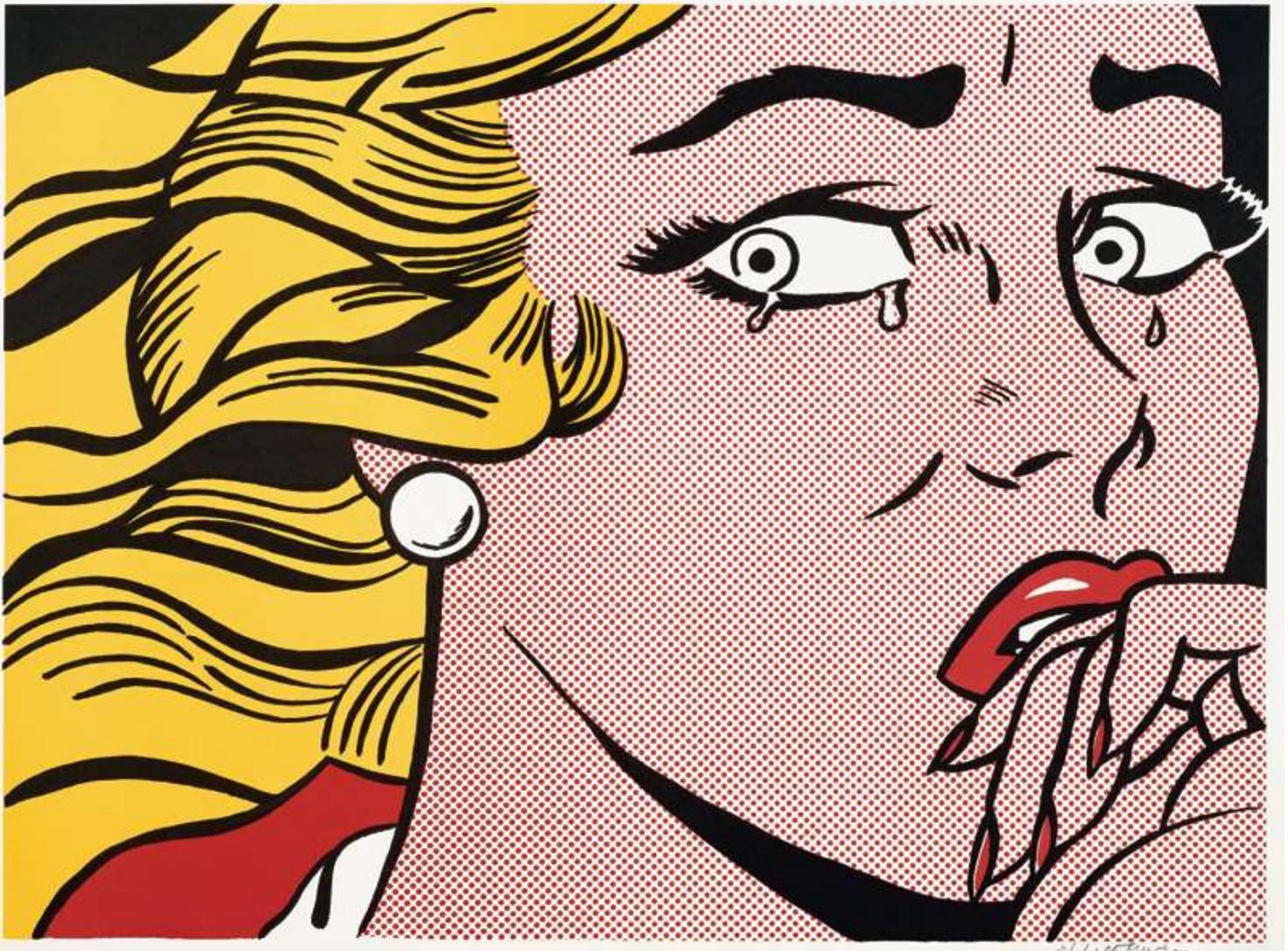


FLUOXETINE



"Crying Girl", oil and synthetic polymer on canvas, 1963, Roy Lichtenstein.

The late Twentieth century witnessed are-embrace of biology as the basis of mental illness and an increasing neglect of its other dimensions....Parents and their families learnt to attribute mental illness to faulty brain biochemistry, defects of dopamine or a shortage of serotonin. It was biobabble as deeply misleading and unscientific as the psychobabble it replaced - in reality the major forms of madness remain almost as mysterious as ever - but as marketing copy it was priceless. Meantime the psychiatric profession was seduced and bought off with enormous amounts of research funding. Where once psychiatrists had existed in a twilight zone on the margins of professional respectability (their talk cures and obsessions with childhood sexuality only amplifying

the scorn with which most mainstream medics viewed them), now they were the darlings of medical school deans, the millions upon millions of their grants and indirect cost recoveries helping to finance the expansion of the medical - industrial complex that has been so notable a development of the years since the Second World War. Much of that financing has come from a pharmaceutical industry that has grown to maturity over the past three quarters of a century. Big Pharma is an international phenomenon these days. Its marketing muscle reaches across the globe. Its search for profitable new compounds ignores national boundaries, except so far as it often retreats to the global periphery to conduct its researches, where ethical constraints are more easily evaded, and the information gleaned from multi-centered clinical trials more easily kept under company control. And its profits are astounding, far exceeding those of many other segments of the economy. That the bulk of them are earned in the free-for-all that is the United States is one of the primary reasons for the growing global hegemony of American psychiatry.

For psychiatric drugs have been a central part of Big Pharma's expansion and profits. That is not because we possess a psychiatric penicillin. Quite the contrary: for all the marketing hype surrounding psychopharmacology, its pills and potions are palliative, not curative - and often not even that. But ironically, it is precisely the relative therapeutic impotence of psychotropic drugs that has made them so valuable and has vaulted them so regularly into the ranks of the so-called blockbuster drugs, those that amass north of a billion dollars in profits for the industry. Drugs that cure are great - for the patient. For the pharmaceutical houses, this is not always so. Antibiotics for example, at least until their excessive use in factory farming renders them ineffective, cure bacterial infections in short order. Diseases that a century ago were major, even fatal events are now routinely cured by a single course of treatment. Not so much money there, once the initial excitement subsides, though sales volume makes for profits that are not to be sneezed at. So diseases that can be managed, but not cured, are ideal: diabetes types I and II; hypertension, the buildup of lipids in the bloodstream and the blocking of arteries by cholesterol, arthritis, asthma, acid reflux, HIV infections - these are conditions that linger for years and are the source of potentially immense windfalls. To be sure as patents expire, profits fall but there is always the possibility of tweaking a formula, creating a variant of a patent, perhaps a new class of drugs to prescribe. Chronic conditions are chronically profitable.

Enter psychiatry, whose disorders may be elusive and sometimes controversial, their aetiology still mysterious and poorly understood, but many are persistent, disabling and distressing. They are impossible to ignore, difficult though they may be to understand and to treat. Once new classes of drugs emerged that provided a measure of symptomatic relief (or could be claimed to do so), the potential market was enormous.....But in the immortal words often (wrongly) attributed to the economist Milton Friedman, "there is no such thing as a free lunch" and one must remember that medical treatments of all sorts, even the most efficacious, carry a risk of side effects. That caveat needs to be born in mind when assessing the psychopharmacological revolution and its impact on psychiatry. It will not do to be a Luddite, to scorn or deny such progress as has been made. And yet the problems that have surfaced in the psychiatric arena are multiple and deeply troubling. The lunch on offer has proved very expensive indeed, and for a good many consumers not worth what it costs. Drug treatments in psychiatry are,

unfortunately, not always particularly efficacious, and such efficacy as they do possess has regularly been overstated by psychiatrists and in the scientific literature. The price patients may pay for such benefits as the drugs do provide has, on the other hand, often been underestimated or actively concealed. Part of the problem, particularly in the early years of psychopharmacology, was an abundance of poorly designed studies that systematically biased findings in a positive direction. In later years, the growing power of the pharmaceutical industry, and the lengths to which it has gone in its pursuit of profit, has led informed observers to worry that what appears to be “evidence based psychiatry” might more properly be called “evidence - biased psychiatry”.

Though it took as long as twenty years for the psychiatric profession to acknowledge the fact, the first generation of antipsychotics, the phenothiazines were often associated with profound and disabling side effects. Some patients developed symptoms that resembled Parkinson's disease. Others became constantly restless, unable to sit still. Then there were those who, conversely remained immobile for extended periods. Most serious of all was a condition that came to be called “tardive dyskinesia”...a disorder often masked while taking the drug, that produced sucking and smacking movements of the lips, rocking and uncontrolled movements of the extremities - and ironically, often interpreted by the laity as signs of mental disturbance. Tardive dyskinesia, in particular, afflicted a large fraction of those on long-term treatment (estimates ranged widely from 15-60 per cent of such patients), and was in most cases a hard to reverse, iatrogenic (i.e doctor caused) condition....

The pattern established by this first generation of psychotropic drugs has held good for all those that came after: the various antidepressants, whose introduction sparked a massive expansion in the numbers being diagnosed with depression, making it the common cold of psychiatry, and the so called “atypical antipsychotics” that entered the marketplace two decades ago, a heterogeneous array of pills that had different chemical properties and purported to avoid many of the serious side effects that plagued the phenothiazines. Prozac made people “better than well” , and then it turned out that it did not. It, and related antidepressants called SSRIs are anything but a panacea. Whatever positive effects these drugs have are often outweighed by the problems they create, not least because a number of studies suggest that save, in severe depressions they are barely, if at all superior to placebo. As the Harvard psychiatrist Steven E. Hyman summarizes, the situation remains bleak: even though “many antidepressant drugs have been developed since the 1950s....none of them has improved on the efficacy of the first generation of such drugs, leaving many patients with modest benefits or none at all.

*When SSRI s came to be used in the treatment of children, the **increased** risk of suicidal thoughts and suicide (a side effect long concealed and denied by the drug industry) was initially publicized not by psychiatrists but by investigative journalists working for the BBC in the UK. The National Institute for Health and Care Excellence (NICE), a British Government body charged with appraising the clinical value of new treatments, had been on the brink of endorsing the use of SSRIs in children. It changed its mind and in 2004 recommended against their use. As further negative clinical trial data leaked into the public domain, they eventually prompted the American Food and Drug Administration to require a so-called “black box warning”, of the heightened danger, the most serious*

cautionary flag available short of removing drugs from the market, and the FDA refused to license drugs such as Paxil and Zoloft for use in young people. Later still it emerged that while published studies suggested that SSRIs were effective in treating depression in children and adolescents, the research in question “had been manipulated so that essentially negative studies were transformed into positive studies, hiding the fact that the drugs didn’t work and masking the problems of treatment”. More seriously still, evidence surfaced of just how many studies of SSRIs had been suppressed - all of them negative, and none of them seeing the light of day until outside pressure was brought to bear.

Andrew Scull, “Madness in Civilization”, Princeton, 2015.

In the 1990s fluoxetine, marketed under the trade name of “Prozac”, was one of the biggest selling antidepressant drugs in the world. It made astonishing profits for Big Pharma. It was meant to be the new miracle agent that would make all the first generation agents obsolete over night. Yet with time it proved no more effective than the agents it was supposed to replace, and although not as lethal in overdose it was most definitely not without significant side effects - in particular those of serotonin toxicity. It is interesting to note that among its side effects are anxiety and agitation, and even occasional increased suicidal ideation in children - all effects for which the agent is supposedly a treatment for. Andrew Scull, in his magisterial 2015 book “Madness in Civilization” gives a timely caution against the bright claims of 21st century “Big Pharma”. As patents expire, drugs become less profitable and are quickly replaced by the next “miracle” drug - Big Pharma tells us now that it’s the SNRIs - agents that happen to be significantly more toxic in overdose than the SSRIs!



“Hopeless”, oil and acrylic on canvas, 1963 Roy Lichtenstein

FLUOXETINE

Introduction

Fluoxetine (trade name **Prozac**) was the prototype of the **selective serotonin reuptake inhibitor (SSRI)** drugs.

It is as effective as the first generation agents for the treatment of depression and although not nearly as lethal in overdose as those agents, nonetheless is not without its own significant side effects.

See also separate documents on:

- **SSRI Overdose (in Toxicology folder)**
- **Serotonin Syndrome (in Toxicology folder)**

History

Fluoxetine was developed by Klaus Schmiegel and Bryan Molloy of the Eli Lilly Company in 1972 and was introduced into medical practice in 1986.

The SSRIs were developed in order to have safer less toxic antidepressant agents, than the tricyclic antidepressants or MAOIs that were the front line antidepressants of the 1970s and early 1980s.

Classification

The selective **serotonin reuptake inhibitors (SSRIs)** currently include:

1. **Fluoxetine**
2. Citalopram
3. Escitalopram
4. Fluvoxamine
5. Paroxetine
6. Sertraline
7. Dapoxetine

The **serotonin and noradrenaline reuptake inhibitors (SNRIs)** currently include:

1. Venlafaxine

2. Desvenlafaxine
3. Duloxetine

Preparations

Fluoxetine hydrochloride as:

Tablets:

- 20 mg.

Capsules:

- 20 mg.

Capsules and tablets are bioequivalent.

Mechanism of Action

The SSRIs selectively inhibit the presynaptic reuptake of serotonin (5-hydroxytryptamine, 5HT).

They do *not* block the reuptake of noradrenaline.

Pharmacokinetics

Absorption:

- Fluoxetine is administered orally. It is 80 - 95% absorbed following oral administration.
- There is a linear dose proportionality for the absorption of fluoxetine over the therapeutic dose range.

Distribution:

- The volume of distribution for fluoxetine is estimated at 30-40 L/kg.
- It is about 95% protein bound.
- Fluoxetine can cross the placenta.
- Fluoxetine is excreted into breast milk.

Metabolism and excretion:

- Fluoxetine is extensively metabolised in the liver by multiple cytochrome P450 isoenzymes, including CYP2D6, to norfluoxetine and a number of other, unidentified metabolites.
- Norfluoxetine is an active metabolite.
- Fluoxetine has a longer half-life than the other SSRIs its elimination half-life is 1 - 3 days after acute administration and 4 -6 days after chronic administration.

Its active metabolite norfluoxetine has a half-life up to **16 days**, which can lead to drug interactions long after fluoxetine is stopped.²

It takes some weeks to achieve steady state and to eliminate fluoxetine.

The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine can lead to significant accumulation of these active agents in chronic use.

Pharmacodynamics

Fluoxetine has an efficacy at least equal to that of tricyclic antidepressants and superior to placebo in the treatment of patients who have anxiety and/ or depressive symptoms.

Antagonism of muscarinic, histaminergic and α_1 -adrenergic receptors have been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects of classic tricyclic antidepressant drugs. Fluoxetine binds to these and other membrane receptors from brain tissue **much less** potently *in vitro* than do the tricyclic drugs and so these adverse effects are not expected with the SSRI agents.

Indications

*Indications for the SSRIs in general include:*²

1. Major depression
2. Anxiety disorders:
 - Panic disorder
 - Obsessive compulsive disorder (OCD)
3. Bulimia nervosa
4. Premenstrual dysphoric disorder (or PMT).

For fluoxetine specifically:

5. Post-traumatic stress disorder

Contraindications/ Precautions

These include:

1. Known hypersensitivity to fluoxetine or to other SSRIs
2. Caution with other **serotonergic** agents:
 - Coadministration with other serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as Sumatriptan, or MAOIs - selective, reversible or irreversible - within a minimum of 14 days) may result in **serotonin syndrome**.
3. Bipolar disorder: ²
 - All antidepressants may provoke a manic episode when used in people with **bipolar disorder**.

Some patients *without* a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
4. Dose should be decreased in hepatic impairment:
 - Hepatic impairment further increases the long half-lives of fluoxetine and its active metabolite, norfluoxetine; consider using an alternative SSRI, e.g. citalopram, or use a lower dose and titrate cautiously e.g. 10 mg once daily or 20 mg on alternate days, and titrate cautiously.
5. QT prolongation:
 - QT prolongation can occur with fluoxetine treatment.

Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome; acquired long QT syndrome (e.g. due to concomitant use of a drug that prolongs the QT).
6. Children < 18 years:
 - **Increased** suicidal thoughts and behaviour can occur **soon after** starting any antidepressant, particularly in young people; monitor patients frequently and carefully **early** in treatment.

This is particularly the case with the SSRIs. SSRI use in fact is related to a **higher** overall risk of suicidal behavior in children and adolescents and so SSRIs are **contraindicated** in these age groups.

7. Bleeding risk: ¹

- Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding, especially gastrointestinal bleeding, by blocking the uptake of serotonin into platelets.

However, the absolute risk of this is **low**.

The risk is increased by concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulant drugs and antiplatelet drugs.

Patients with liver cirrhosis or liver failure and patients susceptible to gastrointestinal bleeding (e.g. patients with a history of peptic ulcer disease or oesophageal varices, or who are undergoing surgery) are also at increased risk.

Consider an alternative class of antidepressant or the addition of a gastroprotective drug (e.g. a proton pump inhibitor) in patients at increased risk of bleeding.

If NSAID use must be continued, a less gastrototoxic NSAID is recommended (e.g. ibuprofen, diclofenac).

Pregnancy

Fluoxetine is a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Most studies have shown there is no significant increased risk of congenital malformations following the use of selective serotonin reuptake inhibitors (SSRI) in early pregnancy.

However, newborns exposed to SSRI, especially in late pregnancy, have experienced self-limiting neonatal withdrawal symptoms.

These symptoms include respiratory distress, irritability, temperature instability, sleep disturbance, tremors, jitteriness, feeding difficulties and diarrhoea, which can be attributed to serotonergic hyperstimulation. ⁴

Breastfeeding

SSRIs are used in postnatal depression though some consider sertraline to be the preferred SSRI antidepressant in breastfeeding.²

Fluoxetine is not generally recommended in breast feeding because of its long half-life.²

Small amounts of fluoxetine are excreted into breast milk, but no serious harmful effects have been noted in breastfed infants. Due to the long half-life of fluoxetine, it may result in the slow elimination of the medicine by newborns (particularly in preterm infants). If fluoxetine is the medicine of choice, use the lowest effective daily dose and closely observe the breastfed infant for any adverse effects such as drowsiness, irritability, poor feeding and restlessness.⁴

There is still a lack of information regarding the long term effects on developmental outcomes of infants exposed to fluoxetine via breast milk.⁴

Adverse Effects

These include:

1. Allergic / hypersensitivity reactions.
2. GIT upset:
 - Nausea, diarrhoea
3. CNS effects:
 - Drowsiness/ mild sedation.
 - Serotonergic effects which occur in children > adolescents > adults.

These may include:

- ♥ Anxiety / agitation
 - ♥ Panic attacks
 - ♥ Insomnia
 - ♥ Tremor
4. **Serotonin toxicity :**
 - A more serious serotonin toxicity can develop, particularly when used in combination with other serotonergic agents.

Treatment with either moclobemide or a MAOI (or within 14 days of stopping a MAOI or within 2 days of stopping moclobemide) is contraindicated due to the risk of serotonin toxicity. ²

5. Sexual dysfunction
6. Hyponatraemia:
 - This usually occurs early in treatment, and may be asymptomatic. It is due to SIADH.
7. Prolonged QT interval:
 - Occasionally, fluoxetine may prolong the QT interval and increase the risk of arrhythmia. Avoid use if other risk factors (including other drugs that affect the QT interval) cannot be avoided.
8. Children < 18 years
 - Suicidal ideation may paradoxically be increased

Dosing ²

Major depression:

- 20 mg once daily, gradually increasing if necessary to 60 mg once daily (or in 2 doses in the morning and at midday).
- Use of maintenance doses > 20 mg is not usually necessary.

Obsessive-compulsive disorder, bulimia nervosa:

- 20 mg once daily, increasing as indicated to 60 - 80 mg daily.
- Dose may be divided and given in the morning and at midday in obsessive-compulsive disorder.

Panic disorder:

- 10 mg once daily; do not exceed 20 mg daily.

Premenstrual dysphoric disorder:

- *Continuous treatment*, 20 mg once daily.

- *Cyclic treatment*, 20 mg once daily starting 14 days before the anticipated start of menstruation until the first full day of menses.

Elderly:

- Generally the dose should not exceed 40 mg daily; maximum 60 mg daily.

References

1. eTG - November 2014.
2. Fluoxetine in Australian Medicines Handbook Website, Accessed March 2016.
3. Fluoxetine in MIMs Website 1 January 2014.
4. RWH Pregnancy & Breastfeeding Guidelines, 3 February 2016.

Further reading:

Andrew Scull, “Madness in Civilization: A Cultural History of Insanity”, Princeton, 2015.

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