

CHLORPROMAZINE

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APRIL 1962

THE PRACTITIONER

Founded



in 1868

ROAD ACCIDENTS

**In severe
head injuries**

Largactil
trade mark brand
chlorpromazine hydrochloride

'Largactil' plays an important part in the management of severe head injuries, both initially when high temperatures must be reduced, and subsequently, during a period often lasting many weeks, while the brain stem mechanisms are uncoordinated.

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For contents of this issue see overleaf

"The Practitioner", no 1126, vol. 188, April 1962

The drug business is the most profitable in all of capitalism, journalist Law notes in this scattershot indictment of the pharmaceutical industry, but what do consumers get for the money shovelled into it? A dwindling stream of exorbitantly expensive new drugs, she contends, most of them “me-too” competitors, patent-prolonging reformulations of existing products or marginally effective nostrums for diffuse complaints; vast marketing budgets to cajole consumers into demanding-and doctors into prescribing-unnecessary medications; biased scientific studies and corrupted or intimidated researchers; a regulatory system lobbied and suborned into allowing unsafe and ineffective drugs on the market; and a society that automatically pops a pill for every discontent, real or imagined.

Publishers Weekly, 2006

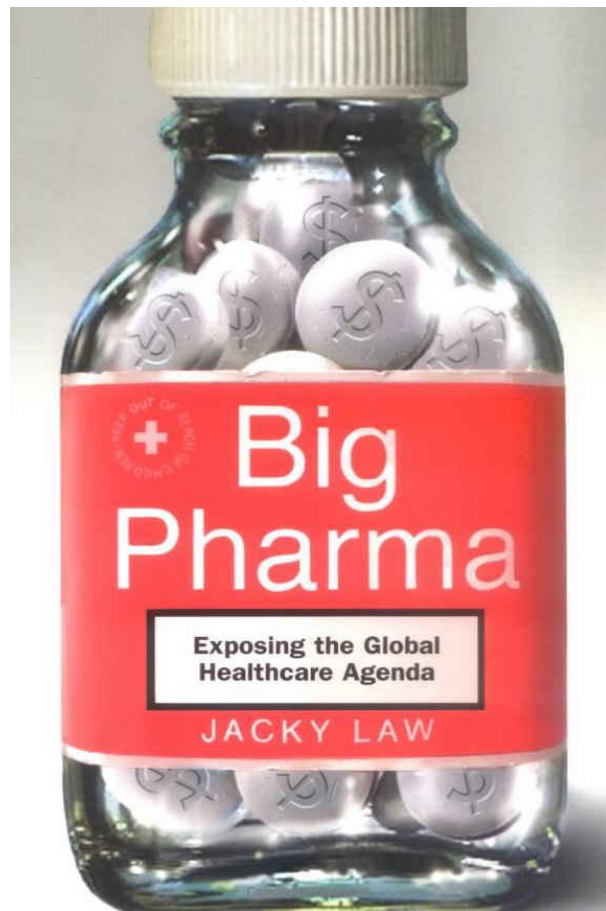
British journalist Law deconstructs the relationship between Big Pharma, on one hand, and medical professionals and patients, on the other, and declares it unhealthy for everybody, though not financially for a handful of major international pharmaceutical companies. How can it be healthy when those companies' annual marketing budgets outstrip the annual budgets of all of the medical schools in the U.S. combined? How can it be healthy when those companies pick and choose which clinical tests of new drugs will be made public? How can it be healthy when the regulating agencies in charge of protecting public health interests are inexorably tied to the pharmaceutical industry? On the other hand, who other than those with ties to pharmaceutical companies can decipher the science-speak of all their reports? And who is to speak for the everyman seeking relief from the pain of everything from real illness to aging? Law's conclusion won't be popular, since she lays the burden on doctors to advocate for their patients, often at the expense of Big Pharma. And while it is some comfort to know that the U.S. isn't alone in its health care woes, it is still darn little comfort.

Donna Chavez Booklist, 2006

In 2006 British journalist Jacky Law created quite a storm with her book, “Big Pharma, exposing the global healthcare agenda” which outlined the profit maximizing agenda of the big pharmaceutical industries. Research and production of new medicines have become driven not by medical needs around the globe but by the agendas of vast profits. One way in which this is done is by the patent-prolonging reformulations of existing products for new indications. In 1950 a wondrous new drug, chlorpromazine changed the face of psychiatric medicine. For the first time in history an effective antipsychotic agent was available which improved the lives of thousands of patients suffering from crippling psychiatric illnesses. Very soon however it was apparent that this agent had a large array of nasty side effects, some, such as the horrific tardive dyskinesia, being irreversible. Although a spectacular breakthrough, it was clear that further work needed to be done. Newer second generation antipsychotic agents became available - just as effective but with far fewer side effects. Older more toxic agents quickly became obsolete. One of these first generation antipsychotic agents however has survived into the 21st century. By 1962 chlorpromazine was being aggressively marketed not as much as an antipsychotic agent, but rather as a newly invented indication for severe head injury!

“The Practitioner” journal of April 1962 makes for fascinating historical reading. The strong influence of drug companies, even that long ago is readily apparent if one flicks

through its pages. A long roll call of vaguely remembered drugs learned as archaic historical anecdotes in medical lectures of the 1980s is seen prominently interspaced among the various medical articles - dextromoramide, meprobamate, tranlycypromine, quinalbarbitone, isoxsuprine, amylobarbitone, dexamphetamine and noscapine. None of these would be familiar to modern day medical students - apart from one - chlorpromazine or Largactil - the original prototype of the first generation of antipsychotic agents. This of course begs the question, how has this toxic agent survived for so long? By 1962, its "indications" had begun to change - first as an agent for use in severe head injury, and the "stabilization of uncoordinated brainstems", but in later years, as a tenuous "second line" agent, for the treatment of conditions as diverse as migraine, serotonin syndrome and hiccups! Medical students of today are barely - if at all - aware that this agent was once the preeminent antipsychotic drug of its day. Some may possibly be aware - but would never have seen - its most feared side effect - tardive dyskinesia. It is clear from the Practitioner Journal of 1962, that the promotion of this agent was very strong - as seen from its prominent display on the frontispiece! Most of the other agents featured in the journal have long since been consigned to the annals of history. Chlorpromazine has been a great survivor - not in its original usefulness as an antipsychotic, but rather in its repeated reinvention for somewhat tenuous indications. "Big Pharma" has been most kind to chlorpromazine!



CHLORPROMAZINE

Introduction

Chlorpromazine, (in Australia, Trade Name, **Largactil**) is a “typical” or first generation antipsychotic drug, generally termed “**major tranquillizers**”.

This agent was traditionally used as a first line drug for acute and chronic psychoses.

However with the availability of safer and more effective antipsychotic agents its prime use is no longer for acute sedation in psychotic patients, however it has retained a tenuous place in current practice for a number of other unrelated indications including:

- Acute migraine
- Anti-hyperthermic agent
- Second line anti-serotonergic agent
- Intractable hiccups

See also separate documents on:

- **Typical Antipsychotic Agent Overdose (Toxicology Folder)**
- **Dystonic reactions (Toxicology Folder)**
- **Neuroleptic malignant syndrome (Toxicology Folder)**

History

Chlorpromazine was developed in 1950. It was the first drug developed with a specific antipsychotic action and served as the prototype of the phenothiazine class of antipsychotic drugs that followed it.

The introduction of chlorpromazine during the 1950s into clinical use for schizophrenia and acute psychoses represented a significant advance in the history of psychiatry.

Chemistry

The first generation (or “typical”) antipsychotic agents consisted of 2 main groups; the **Phenothiazines** and the **Butyrophenones**

Chlorpromazine was an early phenothiazine agent. It is a dimethylamine derivative of phenothiazine.

Preparation

Preparations include:

Tablets: 10 mg, 25 mg, 100 mg.

Liquid: 5 mg/ml, 10 mg/ml

Ampoules: 25 mg/ml in 2 ml ampoules, (total 50mg).

Mechanism of Action

Specific chemical actions include:

1. **Dopamine blockade:**

Antipsychotic actions are thought to be mediated (at least in part) by **blockade of dopaminergic transmission** in various parts of the brain (in particular the limbic system).

Evidence suggests: ²

- All effective antipsychotics block D₂ receptors
- Differential blockade of other dopamine receptors (e.g. D₁) may influence therapeutic and adverse effects
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT₂ antagonism with some agents.

2. Antiadrenergic activity (alpha₁ blocking activity)

3. Peripheral anticholinergic activity.

4. Weak antihistaminic action

5. Weak antiserotonin activity.

Pharmacokinetics

Absorption:

- Chlorpromazine can be given **orally, IV or IM**
- *Avoid* giving IM or SC, as the solution is highly irritant and may cause local necrosis. IM injections are also frequently painful.
- IV doses are best given by infusion and well diluted, with close monitoring.
- Oral dosing:

- ♥ Chlorpromazine is subject to extensive first-pass metabolism in the gut and the liver.
- ♥ Oral absorption is erratic and incomplete with anywhere from 10 - 80% of the dose reaching the systemic circulation. There is wide inter- subject variation.
- ♥ Following oral administration, peak plasma levels are reached in 1 - 4 hours.

Distribution:

- Chlorpromazine is widely distributed to the body tissues.
- It crosses the blood-brain barrier and achieves higher concentrations in the brain than in the plasma.
- Is excreted in breast milk in variable amounts.
- The average Vd is quite large, ranging from 10-35 L/kg (with a mean of 22 L/kg).
- It is highly protein bound (90-99%).
- Chlorpromazine has been detected in urine for up to one year after discontinuation of *chronic* administration.

Metabolism and excretion:

- Chlorpromazine is almost completely metabolised in the liver with less than 1% excreted in the urine as unchanged drug.
- It has multiple metabolites, some of which are biologically active.
- There is wide variation in the elimination half-lives, and a large degree of inter - patient variability.
- There may be *several* elimination phases, consisting of an early phase of 2-3 hours, an intermediate phase of 15 hours and a late phase of up to **60 days**.

Pharmacodynamics

Therapeutic effects include:

1. Anti-psychotic effects
2. Sedation
3. Anxiolysis

4. An antiemetic effect.
5. Anti-pyretic:
 - Phenothiazines depress the mechanism for regulation of temperature, and may be used to help control fever, by stopping shivering.
 - This use is usually in relation to severe hyperthermia reactions, and not routine control of undifferentiated pyrexia.

Indications

Principle indications in the **ED** include:

- Acute migraine
- Anti-hyperthermic agent
- Second line anti-serotonergic agent
- Intractable hiccups

Contraindications/ Precautions

These include:

1. Patients with reduced conscious state (unless the airway is protected)
2. Hypotensive patients
3. Known hypersensitivity to phenothiazines
4. Parkinson's disease:
 - Risk of aggravation
5. Caution in patients with epilepsy - may lower seizure threshold.

Pregnancy

Chlorpromazine is a category C class drug with respect to pregnancy

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

Breast feeding

Caution is advised (insufficient data).

Adverse Effects

Adverse effects include:

1. CVS effects:
 - Hypotension:
 - ♥ Alpha-receptor blockade results in vasodilation
 - ♥ Orthostatic hypotension can occur in ambulant patients
 - ♥ Synergistic action with other drugs that can cause hypotension.
 - QT prolongation (rare)
2. Respiratory:
 - Some respiratory depression
 - Synergistic with other CNS depressants.
3. CNS:
 - Excessive sedation:
 - ♥ Including synergistic effects with other CNS depressants.
 - Seizures:
 - ♥ May lower convulsive threshold in the pre-disposed
 - Hypothalamic effects:
 - ♥ Impaired thermoregulation
 - ♥ Weight gain
 - Extrapyrarnidal effects:

As with any major tranquillizing agent these can include:

 - ♥ Dystonic reactions
 - ♥ Tardive dyskinesia (with chronic use):

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the **duration** of treatment and the **total cumulative dose** of the drug increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. The risk seems to be greater in elderly patients. ⁴

♥ Akathisia:

A feeling of motor restlessness; usually occurs 2- 3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased; agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced. ²

♥ Parkinson's type syndromes:

Includes tremor, rigidity or bradykinesia; usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic (benztropine or benzhexol) may help.

4. Neuroleptic malignant syndrome
5. Chemical inflammation/ necrosis and sterile abscess formation if given IM
6. Anticholinergic effects:
 - Tachycardia/ dry mouth/ blurred vision/ aggravation of narrow angle glaucoma/ urinary retention/ reduced GIT motility - constipation.

Less commonly:

7. Endocrine:
 - May stimulate the release of prolactin
 - Reduced glucose tolerance
 - Inappropriate ADH secretion
8. Immunological:
 - Allergic reactions:

♥ Chlorpromazine injection contains bisulfite and metabisulfite as antioxidants. These excipients can occasionally cause allergic reactions.

♥ Avoid skin contact with the injection solution as there is a risk of contact dermatitis.

- Autoimmune skin reactions, (TEN and variants).
- Phototoxic skin reactions.

9. Cholestatic jaundice

Dosing

For current ED indications:

Acute migraine:

Give:

- 25 mg in 1000 mls of normal saline or Hartman's solution **IV** over 60 minutes (to help avoid hypotension).⁵

Alternatively:

- 12.5 mg in 500 mls of normal saline or Hartman's solution **IV** over 30 minutes
- And repeat once if necessary.

IM administration is thought to be less effective.

Anti-hyperthermic agent:

12.5 – 25 mg can be given by slow IV infusion: in 100 mls normal saline over 30 - 60 minutes.

Hiccups

The following is one recommendation for the treatment of intractable hiccups:⁷

- Chlorpromazine 50 mg via continuous IV infusion over 24 hours.

Second line anti-serotonergic agent

- Chlorpromazine has some anti-serotonin activity and so may be useful for sedation in severe cases or when oral medication (i.e. first line Cyproheptadine) is unable to be taken.

- **25mg** (- 100mg) can be given by slow IV infusion: in 100 mls normal saline over 30- 60 minutes.⁶

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June 2014.