

# The Technology of Medicines

Peter Pratt

Chief Pharmacist

Sheffield health & Social Care NHS Trust

[Peter.Pratt@shsc.nhs.uk](mailto:Peter.Pratt@shsc.nhs.uk)

# Disclosure statement

- NHS Salary
- Travel expenses ( standard mileage) paid by NAPICU
- Member NICE violence GDG
- No external financial or “benefits in kind”
- Content entirely personal - No external influence whatsoever.
- Session Brief from organisers= Pharmaceuticals & medicines technology & psychiatry

# What's technology got to do with medication?



[Ph. Eur. 7](#) (Chlorpromazine Hydrochloride).

A white or almost white crystalline powder.

It shows polymorphism.

It decomposes on exposure to air and light.

Very soluble in water; freely soluble in alcohol.

A freshly prepared 10% solution in water has a pH of 3.5 to 4.5.

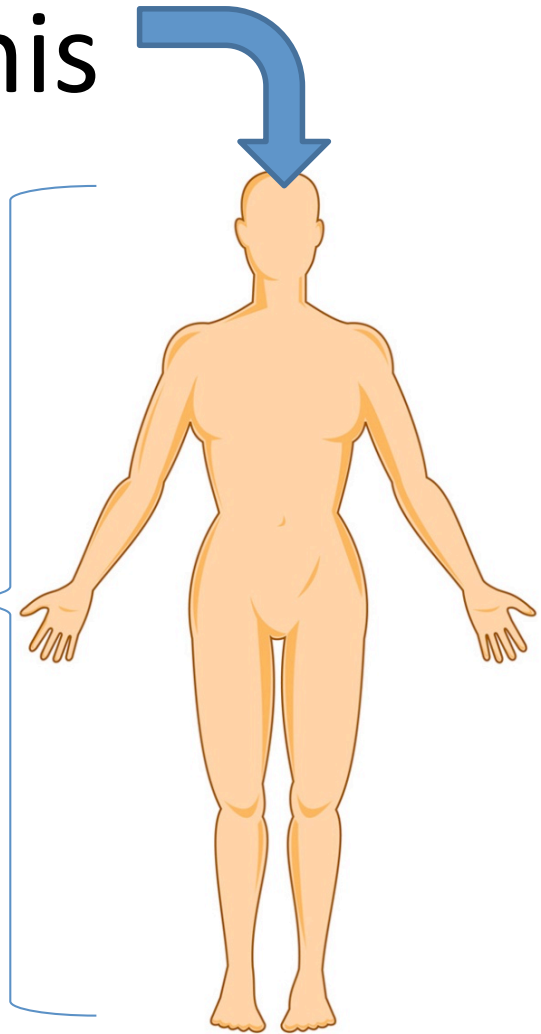
Store in airtight containers. Protect from light.

We need Technology  
to

get this into this



Don't forget the  
Technology of "us"



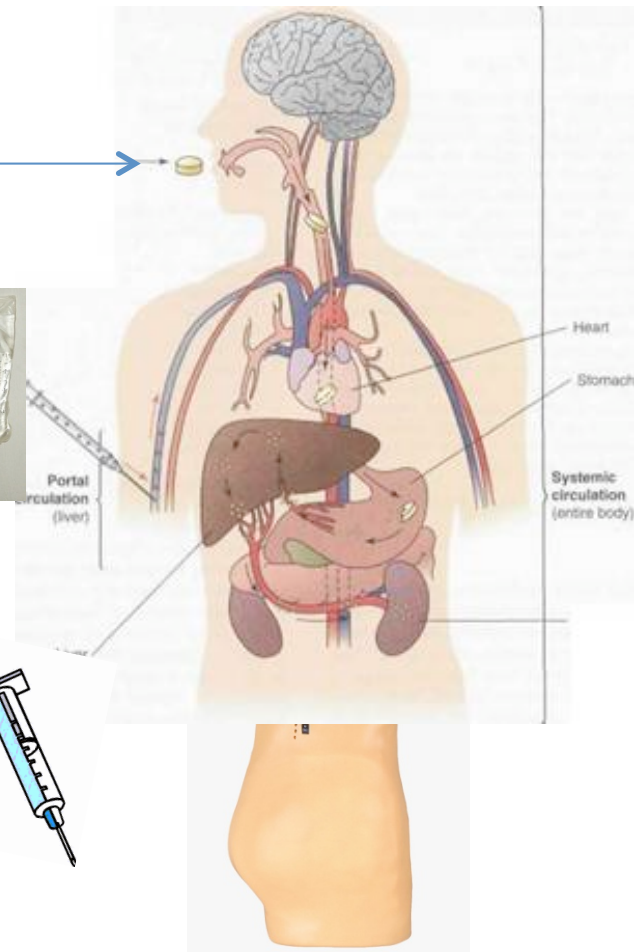
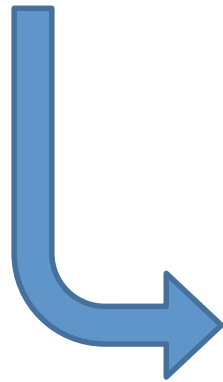


+ Lactose monohydrate+povidone+magnesium stearate+maize starch

Plus

Polyvinylacetate phthalate+stearic acid+talc+calcium carbonate+acacia  
+titanium dioxide (E171)+sucrose+shellac+yellow carnauba wax+white beeswax.

Sodium sulphite anhydrous (E221) +Sodium citrate +Sodium metabisulphite (E223) + Sodium chloride +Water for Injections



# Can technology help?

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**WARNING!**  
**MENTAL PATIENTS ARE NOTORIOUS**  
**DRUG EVADERS\***

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Many mental patients "cheek" or hide their tablets and then dispose of them. Unless this practice is stopped, they deprive themselves of opportunities for improvement or remission . . . deceive their doctors into thinking that their drugs have failed . . . and impose a needless drain on their hospital's finances.

When drug evaders jeopardize the effectiveness of your treatment program—

# Old Technology overcomes problems of not taking tablets

Ph. Eur. 7 (Chlorpromazine Hydrochloride).

A white or almost white crystalline powder.

It shows polymorphism.

It decomposes on exposure to air and light.

**Very soluble in water; freely soluble in alcohol.**

A freshly prepared 10% solution in water has a pH of 3.5 to 4.5.

Store in airtight containers. Protect from light.

## **A saboteur who deserves help**

Mental patients who fear or resent medication throw away thousands of dollars in drugs each year.

Unhelped by drug therapy, they often pose a difficult management problem. And they sabotage the progress of other patients by spreading fears and multiplying conflicts on the hospital ward.

You can virtually assure these patients the benefit of drug therapy with 'Thorazine' Concentrate. Easy to administer, 'Thorazine' Concentrate cannot be "cheeked" and disposed of later; it provides dependable control of agitation and hyperactivity.

## **You can help him with Thorazine® Concentrate**

brand of chlorpromazine

*Contraindications:* Comatose states or the presence of large amounts of C.N.S. depressants.

*Principal Side Effects:* The most frequently encountered side effect is transitory drowsiness. Other occasional side effects include: dry mouth, nasal congestion, constipation, mild fever, miosis, dermatological reactions, extrapyramidal symptoms, weight gain, hypotension and, less frequently, jaundice. Side effects which occur rarely include: mydriasis, pigmentation, ocular changes and agranulocytosis.

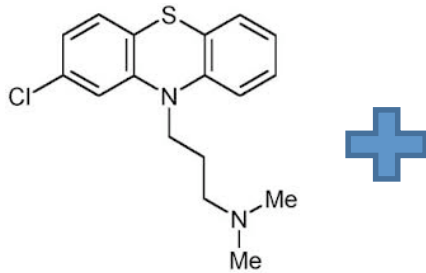
Before prescribing, see SK&F product Prescribing Information.



Smith Kline & French Laboratories, Philadelphia



# Old technology to improve compliance



benzyl alcohol+calcium sulfate  
 +cetylpyridinium chloride  
 +FD&C Yellow No. 6  
 +gelatin+glyceryl distearate  
 +glyceryl monostearate  
 +iron oxide+povidone+silicon  
 dioxide+sodium lauryl sulfate  
 +starch+sucrose+titanium dioxide  
 +wax  
 +trace amounts of other inactive  
 ingredients.



ALL DAY      Smith, Kline & French Laboratories, Philadelphia, Pa.      ALL NIGHT

## THORAZINE\* SPANSULE† CAPSULES

S.K.F. ANNOUNCES ALL-DAY OR ALL-NIGHT 'THORAZINE' THERAPY WITH A SINGLE ORAL DOSE

New "Thorazine" Spansule capsules offer the proven efficacy of "Thorazine" plus the advantages of all-day or all-night therapy with a single oral dose. Your patients will enjoy the convenience of only one or two doses daily. There is little risk of forgotten doses and consequent medication-free intervals. For the discharged mental patient on maintenance therapy, "Thorazine" Spansule capsules will eliminate the trouble and embarrassment of taking tablets at work.

Thorazine Spansule capsules help hospital personnel save time in busy wards. Patients who require tablet medication three or more times daily can obtain the same therapeutic benefits with only one or, at the most, two doses daily.

To give you optimum flexibility in selecting and adjusting dosages for your individual patients, "Thorazine" Spansule capsules are available in four strengths: 30 mg., 75 mg., 150 mg. and 200 mg.

Convenient Dosage Form  
 "Spansule" capsules provide sustained release of medication over a prolonged period of time. In each capsule, hundreds of tiny, coated pellets with varying disintegration times assure a release of medication which is uniform, continuous and prolonged—regardless of individual variation in pH and motility of the intestinal tract.

Thorazine's Usefulness Enhanced  
 With the introduction of "Thorazine" Spansule capsules, Thorazine's usefulness is extended, providing sustained therapy in all indications where "Thorazine" has proved its value.

Four Strengths Offered  
 New "Thorazine" Spansule capsules are available in four strengths—30 mg., 75 mg., 150 mg. and 200 mg.—to facilitate individual dosage regimens. In many cases, a single dose in the morning will achieve the desired response. When 24-hour therapeutic effect is desired, the morning dose may be repeated in the late afternoon or evening.

Only one or two doses daily save time in busy wards where three or four "dosage rounds" with tablets were required.

\*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.  
 †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

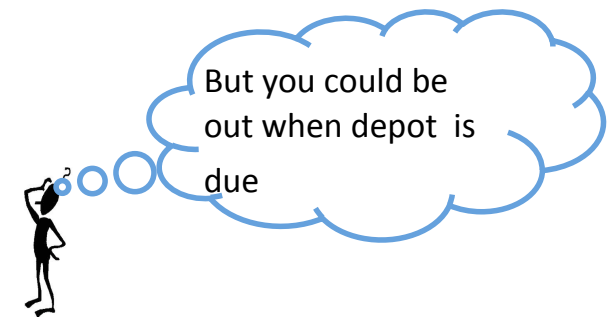
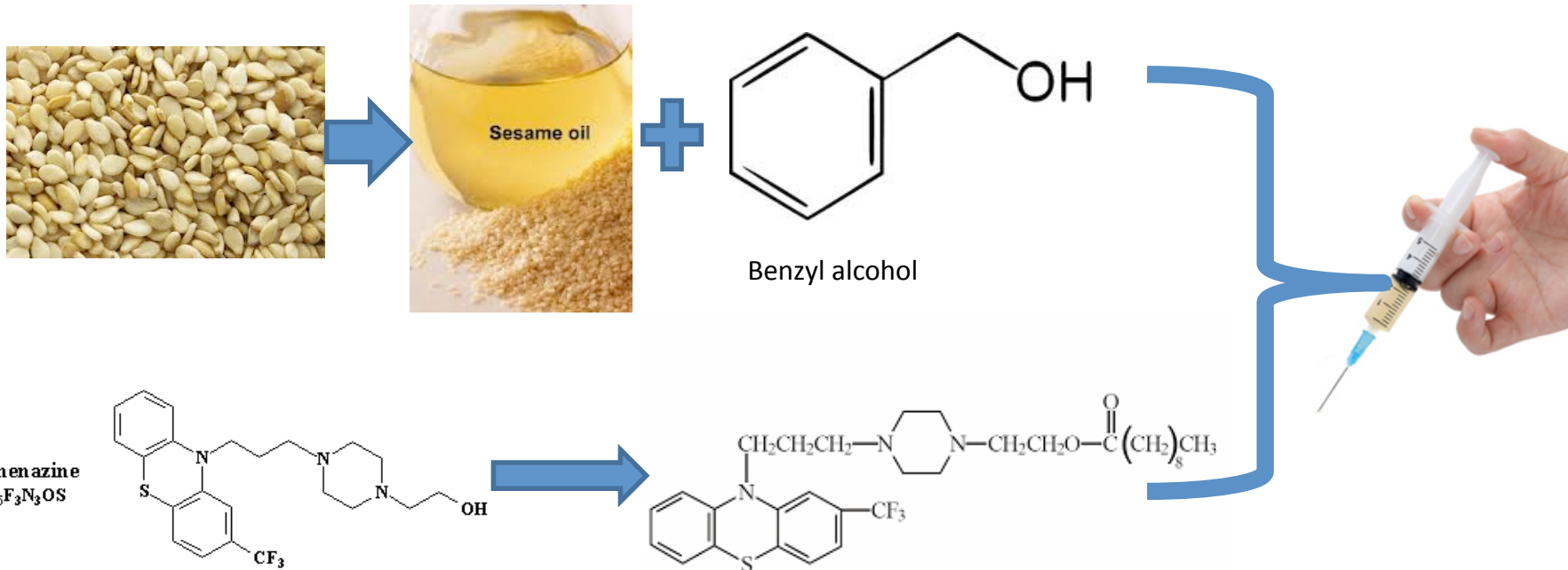
“Your patients will enjoy the convenience of only one or two daily doses... there is little risk of forgotten doses”

Half life around 24 hours?

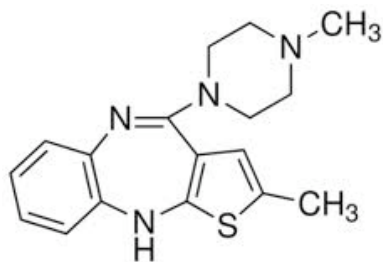




# Old technology to improve compliance



# Old New technology to improve compliance



Gelatin +Mannitol (E421)+Aspartame (E951)  
 +Sodium methyl parahydroxybenzoate (E219)  
 +Sodium propyl parahydroxybenzoate (E217)

But you still have to swallow



**Abbreviated Prescribing Information: Presentation:** Tablets: 2.5mg, 5mg, 7.5mg or 10mg of citalopram. Also contain lactose. VeloTab: 5mg and 10mg orally disintegrating tablets. Also contain gelatin, aspartame, mannitol and parahydroxybenzoates.

**Uses:** Selective serotonin reuptake inhibitor, both as initial therapy and for maintenance.

**Dosage and Administration:** 10mg/day orally. May subsequently be reduced to 5-20mg daily. Children: Not recommended under 18 years. The elderly: A lower starting dose (5mg/day) is not routinely indicated but should be considered when clinical factors warrant. Renal and/or hepatic impairment: 5mg starting dose in moderate hepatic insufficiency. When more than one factor which might cause slower metabolism (female gender, elderly age, non-smoking status), consider a decreased starting dose.

**Contraindications:** Known hypersensitivity to any ingredient. Known risk of neuroleptic malignant syndrome.

**Warnings and Special Precautions:** Clinical monitoring advisable in diabetic patients and those with risk factors for diabetes. Caution with prostatic hypertrophy or paralytic ileus and related conditions. Improvement in clinical condition may take several days to some weeks. Phenytoin: VeloTab contains aspartame — a source of phenylethylamine. Sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate: VeloTab contains these preservatives, known to cause urticaria, contact dermatitis and, rarely, immediate reactions with bronchospasm. Caution in patients with elevated ALT and/or AST, hepatic impairment, limited hepatic functional reserve, and in patients being treated with hepatotoxic drugs. Where hepatitis has been diagnosed, discontinue citalopram. Caution in patients with low leukocyte and/or neutrophil counts, bone marrow depression, and in patients with hypersensitivity conditions or with myeloproliferative disease. Discontinue if signs and symptoms indicative of SJS, or unexplained high fever. Caution in patients who have a history of seizure or are subjected to factors which may lower the seizure threshold. If tardive dyskinesia appears, consider dose reduction or discontinuation. Caution when taken with other centrally acting drugs and alcohol. May antagonise effects of dopamine agonists. Blood pressure should be measured periodically in patients over 65 years. As with other antidepressants, caution when prescribed with drugs known to increase QTc interval, especially in the elderly. In clinical trials, citalopram was not associated with a persistent increase in absolute QT intervals.

**Interactions:** Metabolism may be induced by concomitant smoking or carbamazepine therapy. Metabolism may be inhibited by fluvoxamine or other P450-1A2 inhibitors.

**Pregnancy and Lactation:** Should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Patients should be advised not to breast-feed an infant if they are taking citalopram.

**Driving, etc:** May cause somnolence. Patients should be cautioned about operating hazardous machinery, including motor vehicles.

**Undesirable Effects:** Very common (>10% in clinical trials): Somnolence, weight gain and, in Alzheimer's disease patients, abnormal gait. Common (1-10%): Dizziness, increased appetite, xeroderma, orthostatic hypotension and mild, transient anticholinergic effects, including constipation and dry mouth. Transient, asymptomatic elevations of hepatic transaminases, ALT, AST. Citalopram-treated patients had a lower incidence of parkinsonism, akathisia and dystonia compared with haloperidol-treated patients. Non-fasting plasma glucose levels  $\geq 11\text{mmol/l}$  (suggestive of diabetes) as well as non-fasting levels  $\geq 9\text{mmol/l}$  but  $< 11\text{mmol/l}$  (suggestive of hyperglycaemia) in patients with baseline non-fasting glucose levels  $\leq 7.8\text{mmol/l}$  have been seen occasionally in clinical trials. Uncommon (0.1-1.0%): Photosensitivity reaction and bradycardia, with or without hypotension or syncope. Rare (<0.1%): Rash. Seizures (usually when a history of seizure or risk factors for seizure). Plasma prolactin levels were sometimes elevated but associated clinical manifestations were rare. Cases reported as NMS and cases of high creatine phosphokinase levels have been reported rarely. Very rare (<0.01%): Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketonuria or coma, including some fatal cases. Hepatitis and priapism. Haematological variations, such as leucopenia and thrombocytopenia, have been reported occasionally. For further information see summary of product characteristics.

**Legal Category:** POM. **Marketing Authorisation Numbers:** EU/1/95/022/002, EU/1/95/022/003, EU/1/95/022/004, EU/1/95/022/009, EU/1/95/022/010, EU/1/99/124/001, EU/1/99/124/002. **Basic NHS Cost:** £31.70 per pack of 28 2.5mg tablets, £45.74 per pack of 28 5mg tablets, £145.34 per pack of 56 7.5mg tablets, £27.55 per pack of 28 10mg tablets, £35.11 per pack of 56 10mg tablets, £55.10 per pack of 28 5mg VeloTabs, £112.19 per pack of 28 10mg VeloTabs. **Date of Preparation or Last Review:** June 2001. **Full Prescribing Information is Available From:** Eli Lilly and Company Limited, Dextera Court, Chapel Hill, Basingstoke, Hampshire, RG21 5SQ. Telephone: Basingstoke (01256) 315000. ZYPREXA and VELOTAB are Eli Lilly and Company Limited trademarks.

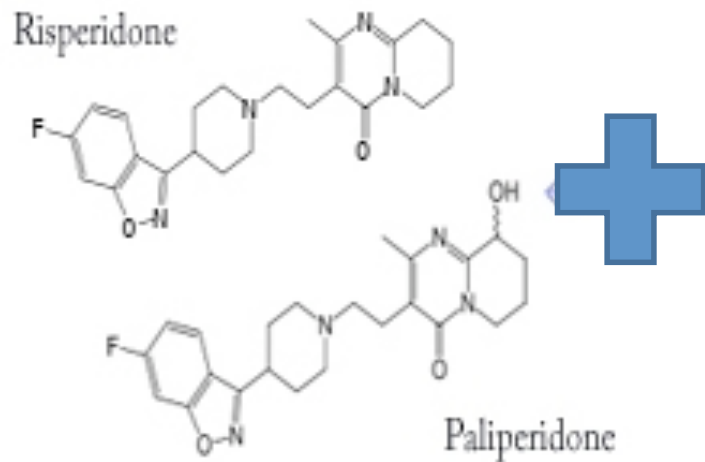
**You're trying to piece her life together**

**She won't swallow it**

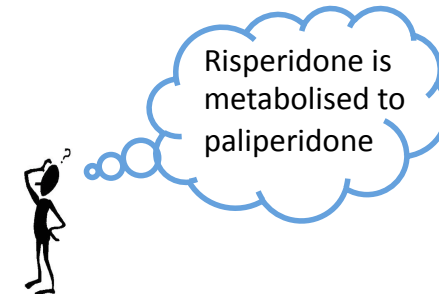
Zyprexa VeloTab™ is a rapidly dissolving tablet of Zyprexa. It helps to overcome the problem of sufferers who need oral therapy but hide their medication or spit it out, helping you to help them when they need it most.

**Removing the obstacles to care** **ZYPREXA VeloTab**

# New(ish) technology to improve compliance

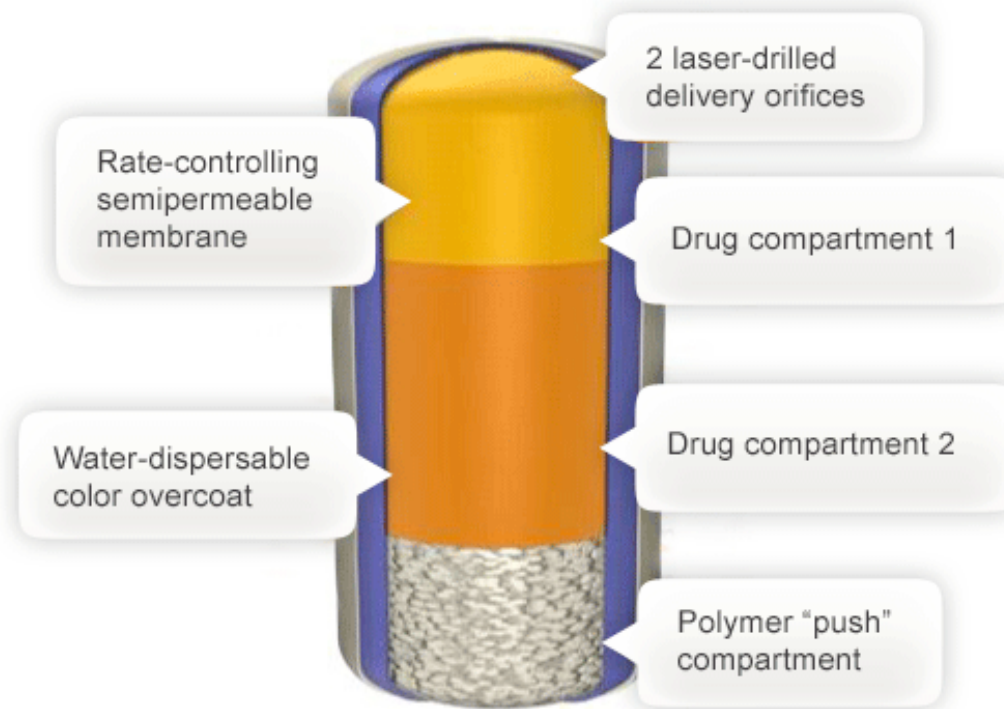


Polyethylene oxide 200K +Sodium chloride+Povidone (K29-32) +Stearic acid  
+Butyl hydroxytoluene (E321)+Iron oxide (black) (E172) +Polyethylene oxide  
7000K  
Ferric oxide (red) (E172) +Ferric oxide (yellow) (E172) (3 mg and 12 mg only)  
+Hydroxyethyl cellulose+  
Polyethylene glycol 3350+ Cellulose acetate  
 $\pm$ Hypromellose+Titanium dioxide (E171)+Lactose monohydrate (3 mg only)  
+Triacetin +Polyethylene glycol +Ferric oxide (yellow) (E172) +Ferric oxide (red)  
(E172)+  
Carnauba wax  
+Printing ink:  
Iron oxide (black) (E172)  
Propylene glycol  
Hypromellose



# 90H risperidone OROS technology

"extended release system...facilitates its once daily use  
and..... *improves treatment compliance*"



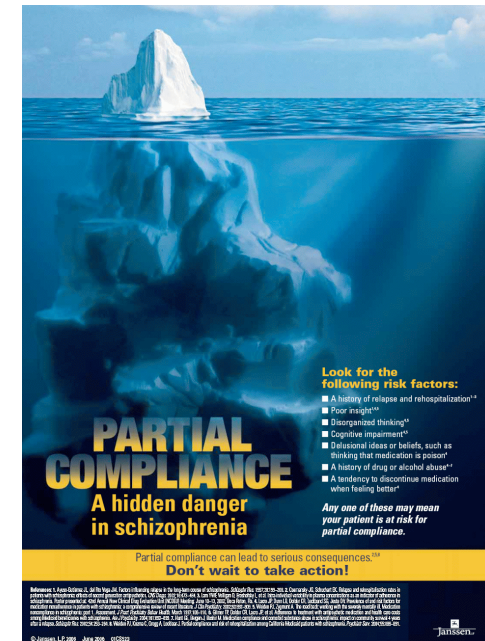
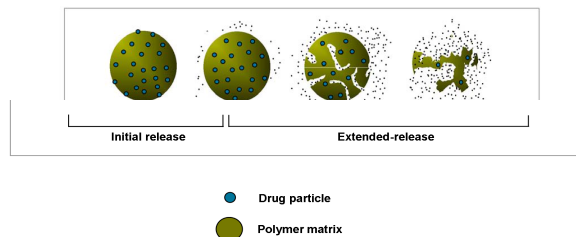
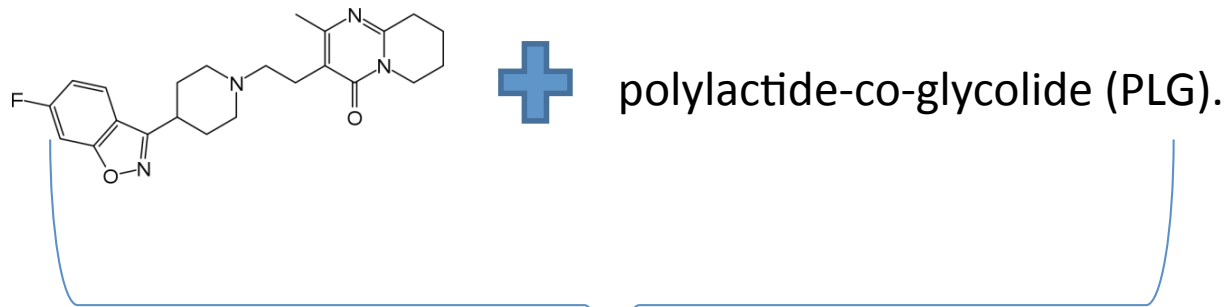
*Osmotic-Controlled Release Oral Delivery System*

Risperidone may be given once or twice daily.



# Old New Technology to improve compliance

Medisorb® drug-delivery technology FROM ALKERMES



PLG is biodegradable polymer used in sutures – also made by Alkermes



# Confidential technology to prevent relapse



Table 1. Composition of Aripiprazole IM Depot (300 mg/vial and 400 mg/vial)

Component	Reference Standard	Function	Quantity (mg/mL) <sup>f</sup>	Quantity per Vial (mg)	
				300-mg/vial	400-mg/vial
Sterile Aripiprazole Monohydrate	In-house	Active	200.0 <sup>a</sup>	375.0 <sup>a</sup>	475.0 <sup>a</sup>
Carboxymethylcellulose Sodium	USP				(b) (4)
Mannitol	USP				
Sodium Phosphate, Monobasic, Monohydrate	USP				
Sodium Hydroxide	NF				
	NF				
Water for Injection, USP	USP				

<http://www.otsuka-us.com/Products/Documents/Abilify.M.PI.pdf>

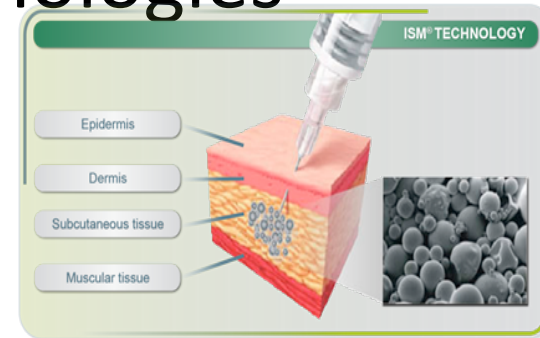


# New Future technology to improve compliance

- ISM<sup>®</sup> technology
  - Rovi Laboratories Risperidone Phase 1 studies
  - Insitu implant formation
  - Solid polymeric matrix contains the drug
  - Reconstituted fluid that precipitates in situ
  - Resulting in the formation of solid or semisolid implants

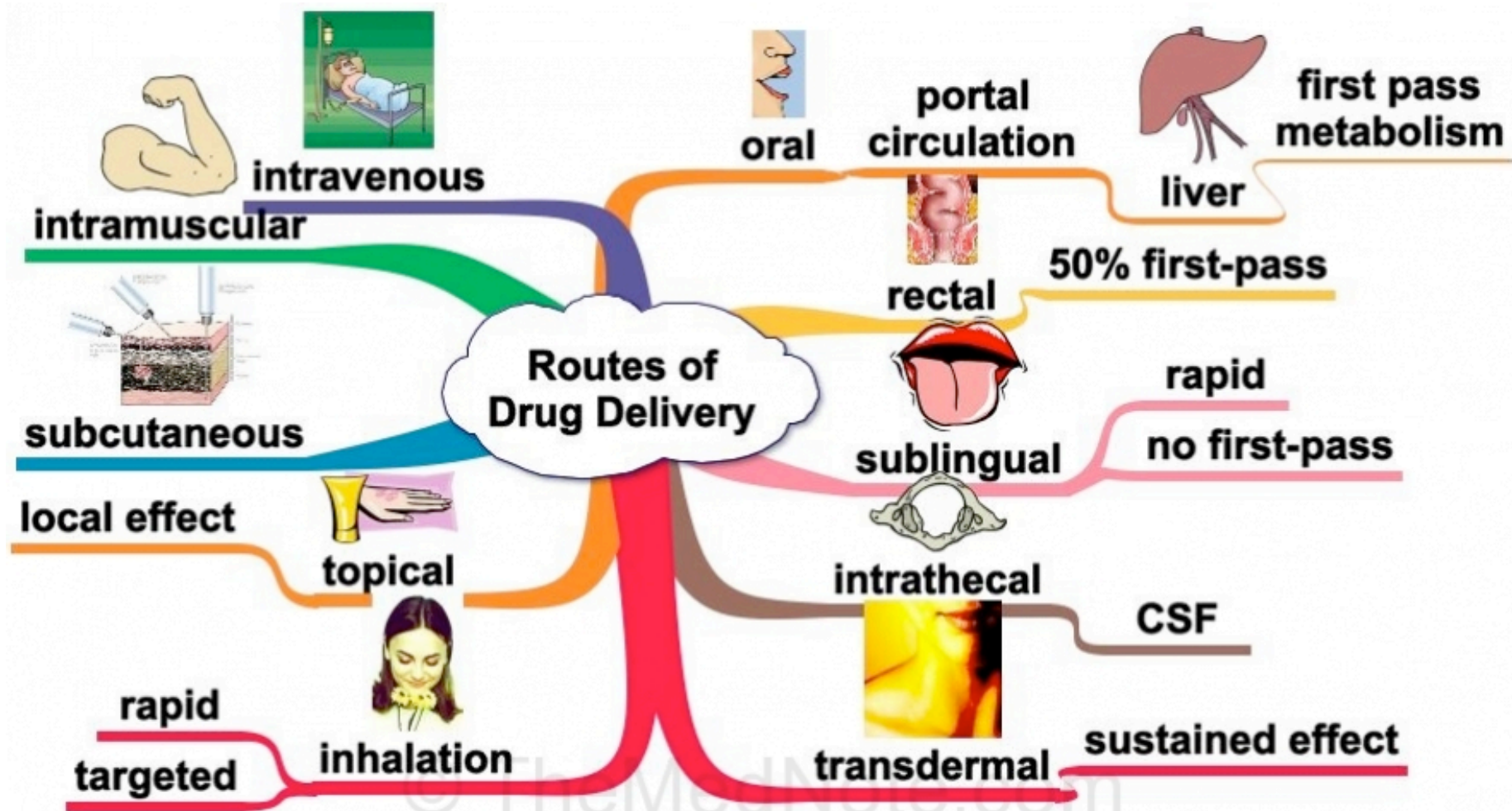
# Claimed Benefit of the Technology

- Advantages over existing technologies
  - Ease of administration
  - Less painful
  - Zero-order kinetics
  - Reduction of the burst effect in drug release
  - Greater reproducibility in the release profiles
  - Highly effective encapsulation+
  - Improvement in the stability of the active substance.

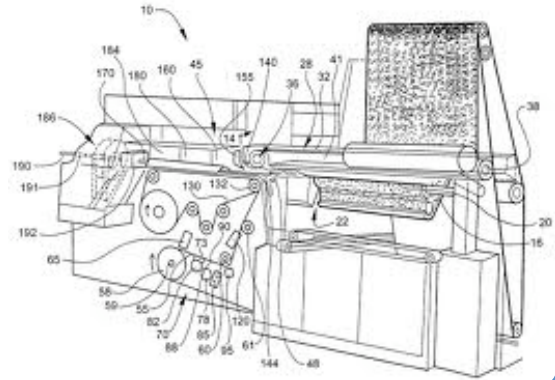




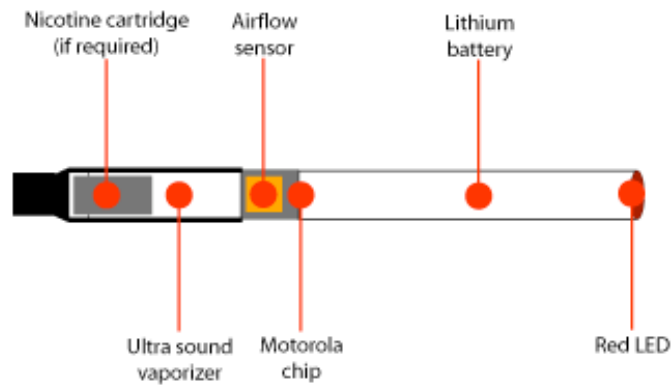
# Technology to assist other routes of administration



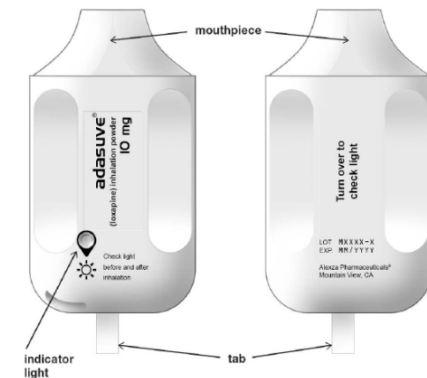
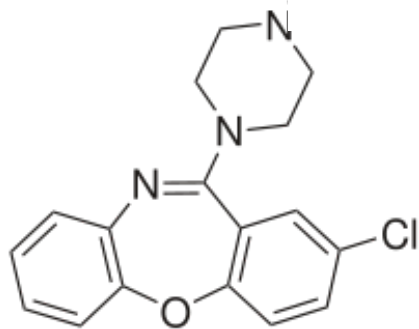
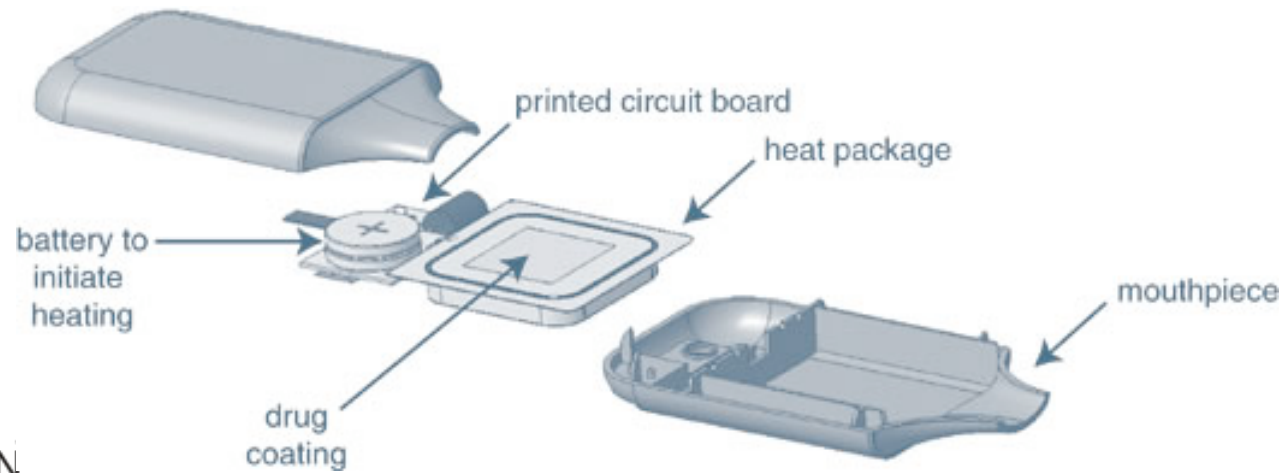
# Very old technology - ensures rapid response



# New technology – rapid response



# Old drug new technology rapid response



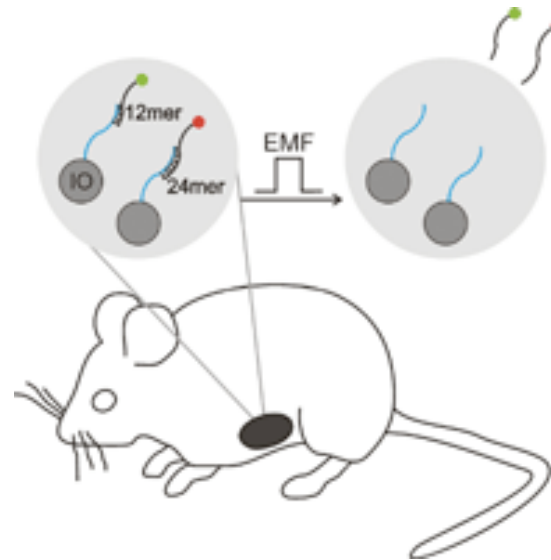
<http://alexza.com/about/the-staccato-system/staccato-animation>

# What is coming up?



# Tomorrows technology

- Nanoparticles made up of Iron oxide containing polymers
- Pores on surface of nanoparticle open up when magnetic field applied – releases drug
- Enables very specific site release of drug
- ?Other uses.....



Thank You

# Lessons from the past.....?

## The Washington Post

2006

"The claims of superiority for the [newer drugs] were greatly exaggerated," wrote Columbia University psychiatrist Jeffrey Lieberman. "This may have been encouraged by an overly expectant community of clinicians and patients eager to believe in the power of new medications. At the same time, the aggressive marketing of these drugs may have contributed to this enhanced perception of their effectiveness in the absence of empirical information."

Peter Jones, a psychiatrist at the University of Cambridge in England who led the study, searched yesterday for the right word to describe what had happened to his colleagues.

" 'Duped' is not right," he said. "We were beguiled."



# Don't forget Alkermes

- Aripiprazole lauroxil (ALKS 9070)
- Depot made from new “LinkeRx “ technology
  - Involves creating new molecules from existing compounds
- Alks 9070 reformulated as aripiprazole lauroxil
  - prodrug for aripiprazole
- P3 Clinical trials to assess release of aripiprazole from ALKS 9070 due completion mid 2014
  - Company claims aripiprazole safety & efficacy already established – only need to establish kinetic profile
- Possible market 2015 ?? UK/EU plans

