MEDICATION DECONSTRUCTION

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PSYCHOPHARMACOL0GY SERIES

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Case study

Teenage girl from a broken home.

Parents, divorced when patient 3 years old, had joint custody.

The girl lived with her mother in another city during the school year and came to her dad for the summer.

Background

doing well in school
no behavioural problems,
no family history of mental illness.
However, after her first breakup, signs of self harm
Superficially cut herself on her forearms.
mother, referred to a community psychiatrist.
Hospitalized, initially diagnosis clinical depression, a diagnosis eventually revised to bipolar disorder.

Medication Hx

After 9 months of treatment, she came to stay with dad who brought her for second opinion
She was on the following regimen:

Lithium 1200 mg/day
Carbamazepine 500 mg/day
Valproate 1750 mg/day
Fluoxetine 40 mg/day
Risperidone 3 mg/day
Benztropine 1 mg/day
Ranitidine 300 mg/day

Treatment review

During interview, the patient was so sedated had to shake her to wake her up.

Insuff. history to confirm a diagnosis of bipolar disorder.

basis for the diagnosis. - extremely agitated in the hospital

Requested the patient's records, which arrived in a couple of weeks.

KEY QUESTIONS TO CONSIDER

1. How can you reconcile the desires of the two custodial parents?

2. Do you leave the patient on her existing regime until the records arrive or go ahead and modify the regimen while waiting for the records?

3. Before beginning to review the regimen, is there any laboratory information you would want?

4. If it is decided to make changes in the regimen, what modification would you make first and why?

1.How can you reconcile the desires of the two custodial parents?

Reducing her medication regimen carried some risk.

But sedation was impairing the patient's functioning.

Balancing the risk of relapse, against excessive sedation

Slow reduction with monitoring for deterioration

Do you leave the patient on her existing regimen until the records arrive or modify it?

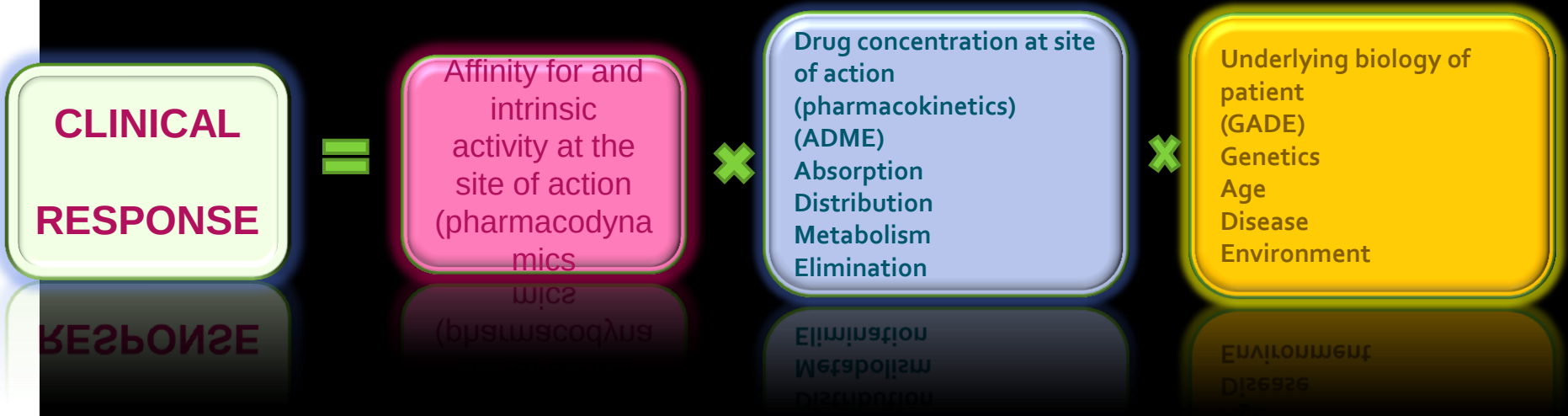
No convincing evidence for bipolar disorder.

Decided to use the lag time to begin the process of modifying the patient's regimen.

Is there any laboratory information needed?

- Therapeutic drug monitoring allows us to measure drug conc, to help determine which drug to discontinue first.
- If drug's conc. is lower than associated with efficacy, then stopping it will make no difference in the outcome.
- If higher concentrations indicate toxicity, again decision about which drug to discontinue first.

Pharmacodynamic and pharmacokinetic equations



$$\text{Concentration} = \frac{\text{dosing rate}}{\text{clearance}}$$

Lab indices

Lithium and valproate levels -within effective range thus helpful in controlling a possible underlying bipolar illness.

Carbamazepine level was below therap range but consistent with the dose.

Fluoxetine and norfluoxetine, were within range expected for the dose being given.

The total levels of risperidone and 9-hydroxyrisperidone (paliperidone), were above the level expected for the dose being given,

Prolactin levels

- serum prolactin level - as an indirect measurement of dopamine-2 (D2) receptor antagonism - not elevated

What modification should be made first?

- Do not precipitate a relapse of a possible underlying bipolar disorder and
- Do not cause a withdrawal reaction or side effect.

Lithium and valproate

-
- decided against discontinuing either lithium or valproate.
- evidence indicate a high likelihood of rapid relapse following rapid discontinuation of lithium in patients with bipolar disorder.
- The decision bolstered by the fact both drugs concentrations within therapeutic range.

Carbamazepine

Levels were below those usually associated with efficacy, thus providing a rationale for stopping this medication.

Inducer of the cytochrome P450 enzyme 3A3/4 , CYP2C9 and CYP2C19–this **increases** the **clearance** of a number of drugs including valproate , possibly fluoxetine and benztropine.

Stopping carbamazepine leads to a loss of CYP 3A3/4 enzyme induction, which would be tantamount to **increasing the dose of those drugs**

Risperidone

The indication not clear, since evidence for psychosis was lacking Moreover, the risperidone levels were at the upper limit of those normally associated with antipsychotic efficacy.

Risperidone was also likely the reason the patient was on benztropine, so that stopping risperidone should eliminate the need forthat drug.

The reason the patient was on benztropine was also not clear, although there are two major possibilities.

Either she had at some point developed extrapyramidal side effects (EPS) (e.g., Parkinsonism, acute dystonia, akathisia), or the previous psychiatrist had added benztropine prophylactically to avoid EPS.

Rationale for EPS

If the patient had developed EPS in the past, that would mean she experienced functionally more D2 receptor antagonism in her basal ganglia than would have been predicted by her plasma concentrations of risperidone plus

9-hydroxyrisperidone and her serum prolactin levels.

That would be a reason for caution in reducing this drug.

Benztropine

One would not want to stop the benztropine until after risperidone was stopped or tapered—otherwise, the patient could be at risk for a recurrence of EPS.

Generally stop D2 receptor antagonists (e.g., risperidone) before discontinuing benztropine, because benztropine clears faster than most D2 receptor antagonists.

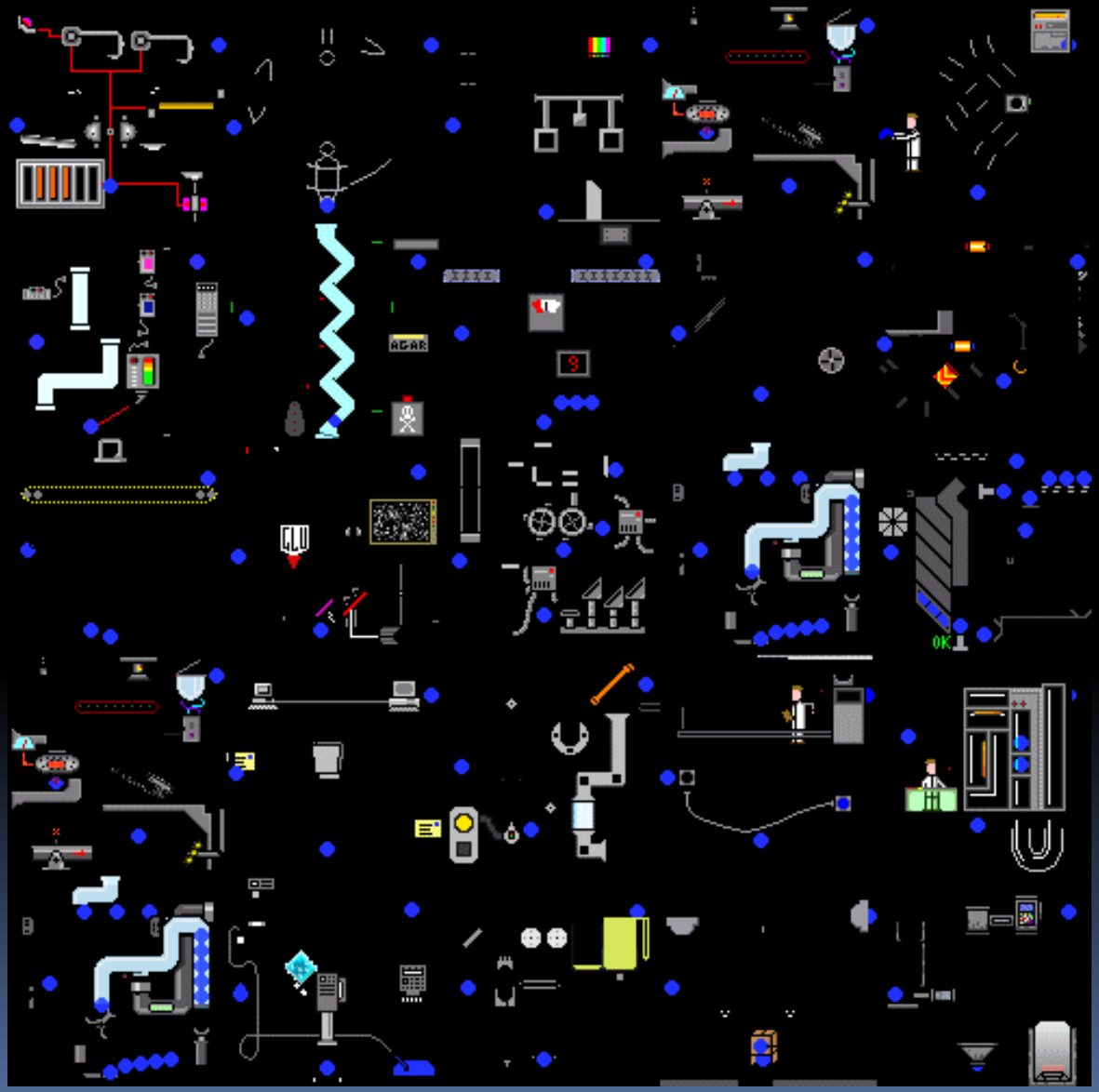
Stopping the benztropine after the D2 receptor antagonist levels have dropped should decrease the risk of a recurrence of EPS.

Ranitidine

Ranitidine was likely given to treat dyspepsia which could be due to lithium, valproate, fluoxetine, and/or carbamazepine.

Hence, this drug would not be stopped until the levels of these drugs were substantially reduced.

Strategy



Fluoxetine

decided first to reduce the fluoxetine, by 50%(i.e., from 40 to 20 mg/day) for the following reasons:

1. fluoxetine has a long half-life, and reducing the dose by half is a conservative course of action one could take.

The drop in the levels of fluoxetine and norfluoxetine would be virtually undetectable for up to a week.

Focus on Fluoxetine

2 Fluoxetine at 20 mg/day is a **substantial** inhibitor of **CYP 2D6**, a **moderate** inhibitor of **CYP 2C19**, and a **mild** inhibitor of CYP **3A3/4.5**,

Since the degree of CYP enzyme inhibition is a function of the concentration of the inhibitor times its potency for inhibiting each CYP enzyme (Equation 2), the magnitude of the inhibition of all of the CYP enzymes listed above would be higher in this patient because of the dose she was taking and the levels that she had therefore accumulated.

CYP 2D6 inhibition and Risperidone levels

CYP 2D6 inhibition is the likely explanation for the risperidone levels being higher than expected given the dose and also for the ratio of risperidone to 9-hydroxyrisperidone being elevated above what would normally be expected.

It might be a useful tool in clinical practice to estimate the possible risk of drug interactions due to impaired CYP2D6 enzyme activity

CYP3A4 is the most abundant drug metabolizing enzyme in humans, and in vitro and in vivo results suggest also a role for the enzyme in risperidone metabolism.

Curr Drug Targets. 2004 Aug;5(6):573-9.

CYP 2D6 inhibition and Benztropine metabolism

There is also some clinical evidence suggesting that benztropine may be partly metabolized by CYP 2D6. *J Pharmacol Exp Ther.* 2007 Jan;320(1):344-53

Thus, reducing the dose and hence concentration of fluoxetine and its metabolite, norfluoxetine, should increase the clearance of risperidone and possibly benztropine

Focus on Fluoxetine

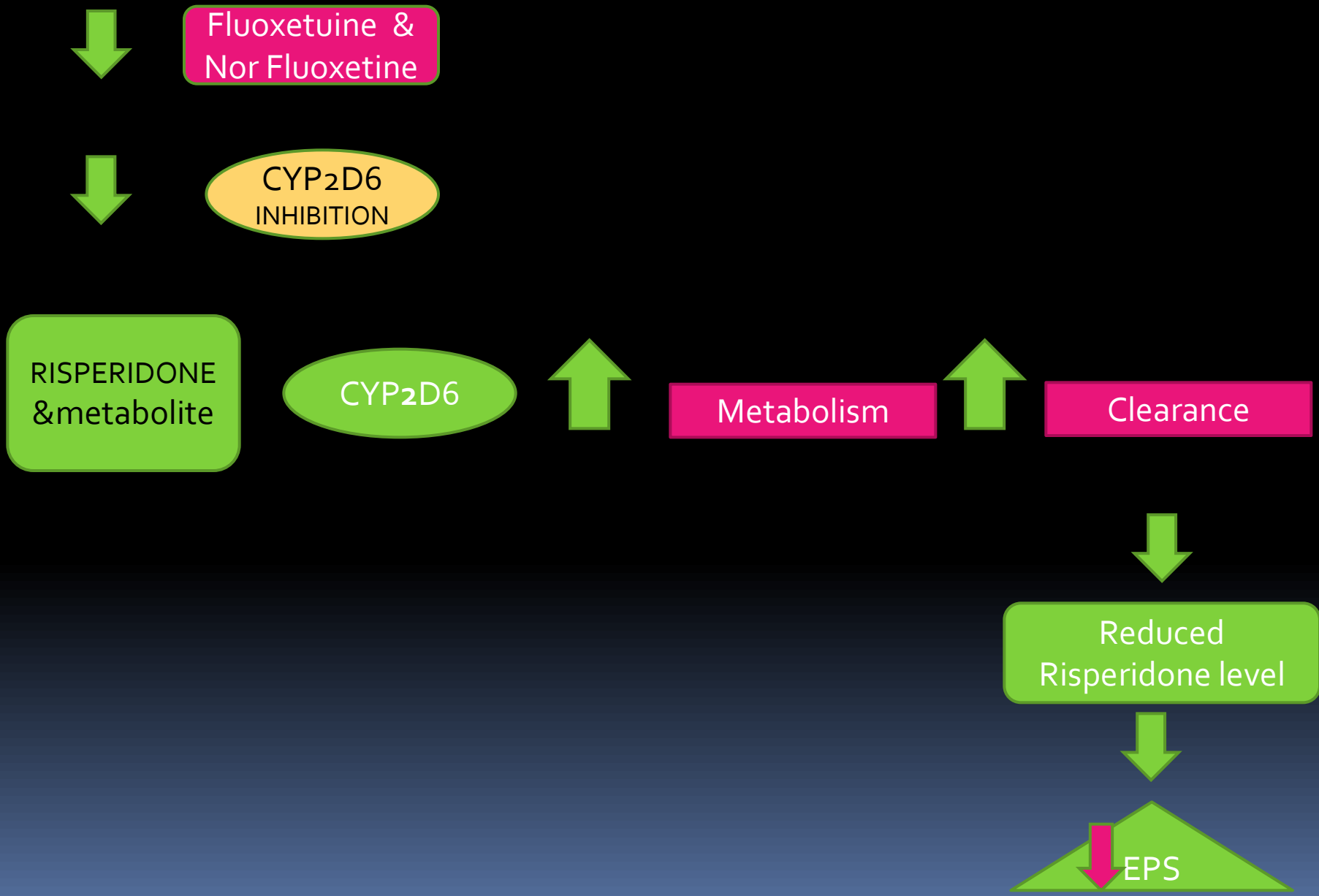
Thirdly Fluoxetine could have contributed to development of EPS in two ways.

i. The inhibition of CYP 2D6 by drugs such as fluoxetine has been identified as a risk factor for the development of EPS on risperidone. *J Am Acad Child Adolesc Psychiatry. 1996 Sep;35(9):1107-8*

ii. Fluoxetine as SSRI , inhibit dopamine cell firing by increasing serotonin inhibitory input to these cells, *Br J Pharmacol. 1995 Sep;116(2):1923-31.*

For both these reasons, the reduction in fluoxetine should further reduce the likelihood of a recurrence of EPS.

Pharmacodynamic /pharmacokinetic pathways



Focus on Fluoxetine

Fourth, fluoxetine as an antidepressant, may worsen cycling in patients with bipolar disorder.

By reducing the dose of fluoxetine, this potential risk might also be decreased. However, data concerning this potential risk with fluoxetine are not compelling.

Finally, fluoxetine causing the dyspepsia, resulting in the need for ranitidine.

Reducing the dose of fluoxetine should decrease the potential need for that drug

Next strategy

The reduction in the patient's fluoxetine dose led to no adverse effects and perhaps a modest increase in the patient's alertness.

Both of these results reassured her parents

Next strategy

The next step was to stop risperidone for the reasons discussed above.

This resulted in no adverse consequences, and the patient may have become somewhat more animated.

Next strategy

The next step was to stop benztropine, which also produced no adverse consequences, and the patient's attention and memory improved.

With risperidone and benztropine stopped, fluoxetine was discontinued without any adverse consequences.

Slow and steady

These changes were made over the first 6 weeks

During this period, her alertness and cognitive abilities improved.

Review of patient's medical records concluded that the patient most likely did not have bipolar disorder, but instead had experienced a manic syndrome resulting from an interaction between paroxetine and buspirone,

Next strategy

Next we stopped carbamazepine and monitored the valproate levels, which rose predicted based on

the known effect of carbamazepine on clearance of valproate

We thus had to reduce the dose of valproate to 1250 mg/day to maintain the same levels that the patient had previously had on 1750 mg/day.

Next strategy

We then began to decrease the dose of valproate, titrating the patient off this medication over the next 3 weeks.

Throughout each of these steps, the patient's alertness and mental functioning continued to improve.

The valproate was discontinued first rather than the lithium because of the remote but real chance that this patient could have a manic relapse.

Need for Ranitidine

With the patient now only on lithium and ranitidine, she was advised to use ranitidine only as needed—and she found she did not need it.

The patient was now taking only lithium and her mental status examination was dramatically improved

Finally ….

After discussion with the patient and her parents the possible risk of reducing the lithium in what we believed was the unlikely scenario that she really had a bipolar disorder.

They had confidence in the process and were ready to proceed.

The patient came off the lithium without problems.

Learning curve 1

Its possible to reduce a medication regime

as well as we can create one

In both situations, we consider the pharmacodynamics and pharmacokinetics of each drug and the potential risks and benefits of stopping each one and in what order.

Learning curve 2

Similarly, we *stopped* only one drug at a time, just as we advocate *adding* only one drug at a time.

This approach allows us to better determine what positive or negative contribution each drug is making to the patient's condition.

Learning curve 3

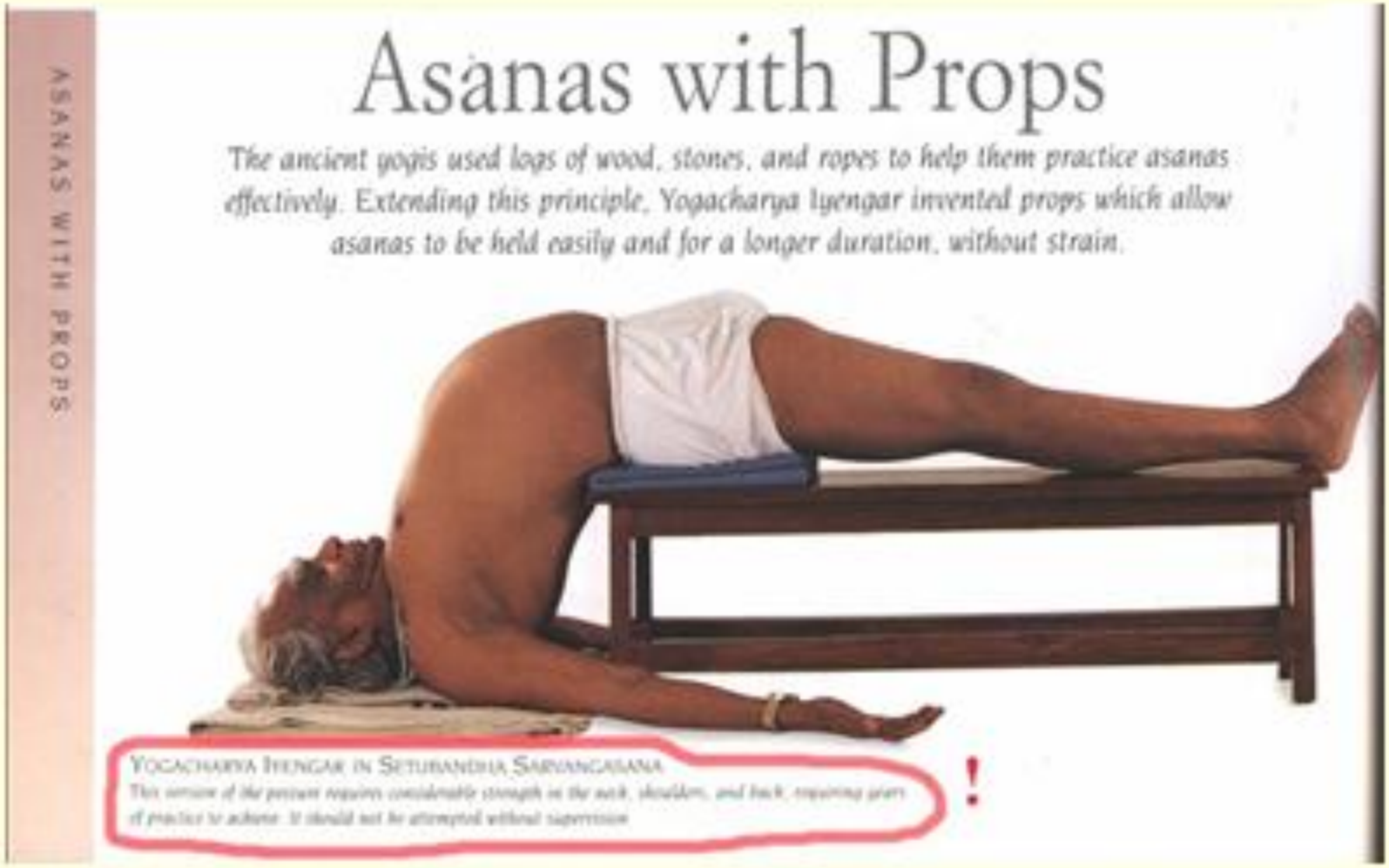
This case illustrates the difficulty to distinguish adverse effects complicated medication regimens from symptoms of the psychiatric illnesses we are trying to treat.

This is because many of these drugs' adverse effects affect the same organ (i.e., the brain) in which the dysfunction responsible for the illness is located.

Learning curve 4

- Always consider whether the patient is experiencing symptoms
  despite the treatment
  or *because of* the treatment
  we are providing.

Yoga for Mental Health



Alternative Yoga

- Next slide

different means ……
……same outcome!!!

Thank you

Guna Kanniah