The Role of Pharmacogenomics in Bipolar and Other Psychiatric Disorders – Case Studies

With a Focus on DDIs

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Psychiatric Case Studies -- Organized Pharmacokinetically

- Carbamazepine (CBZ)
- Phenytoin (PHT)
- Lithium
- Lamotrigine
- Valproate
- Other anticonvulsants
- Analgesic agents
- Various antidepressants and antipsychotic agents

Non-standard abbreviations

CA = cancer

CBZ = carbamazepine

DDI = drug-dependent interaction

PgP = P-glycoprotein

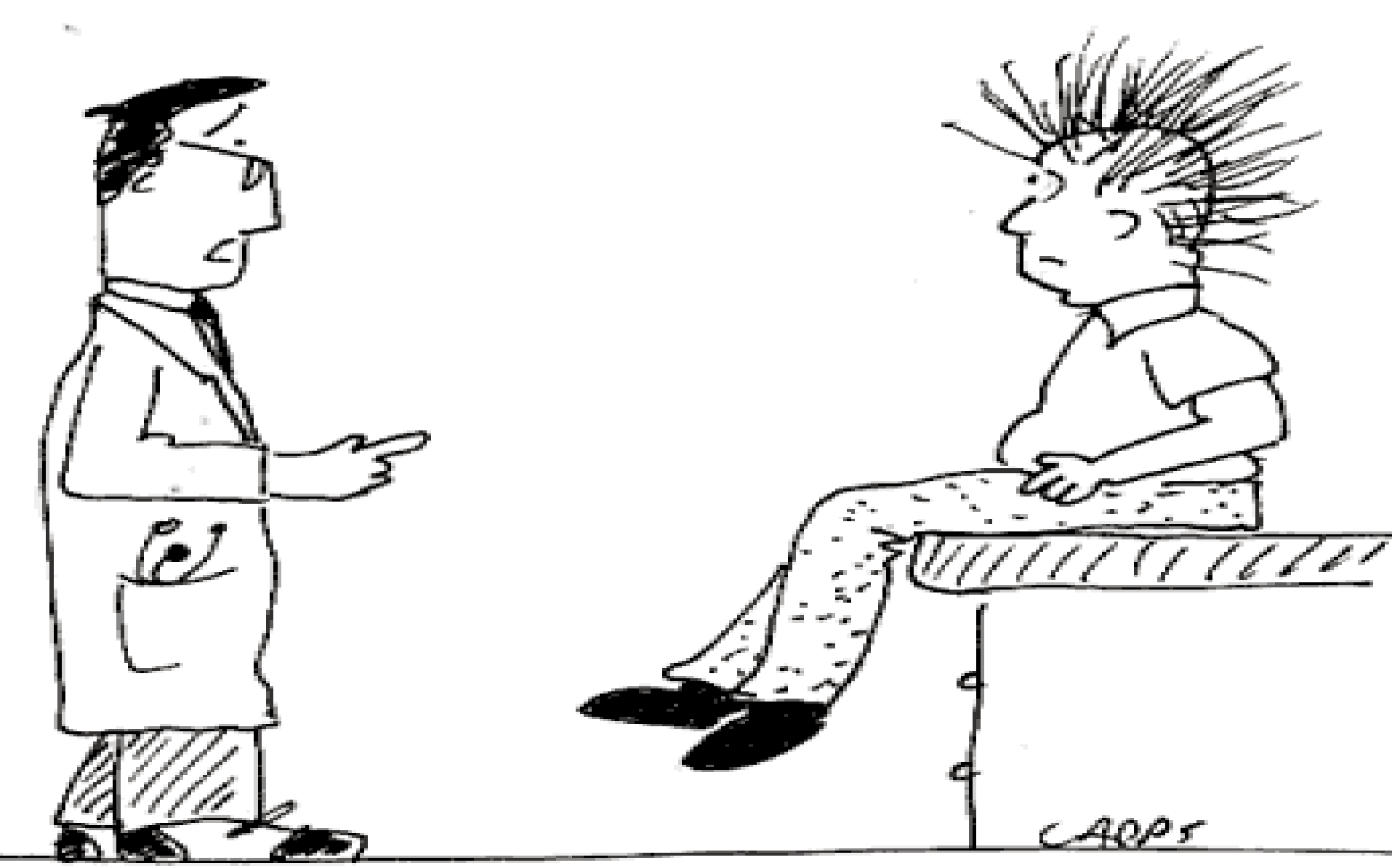
PHT = phenytoin

SJW = St. John's wort

VPA = valproic acid

2D6 Vignette

- **Sad and Sore**
  - Fluoxetine was added to hydrocodone.
  - 2D6 was inhibited.
  - Hydrocodone was not able to be metabolized into hydromorphone.
  - Loss of analgesia resulted.
  - Analgesia returned with removal of fluoxetine.
  - Similar issues encountered with codeine → morphine and tramadol → M1.



"YOU PROBABLY SHOULDN'T MIX YOUR VIAGRA WITH YOUR PROPECIA."

3A4 Vignettes

- **Natural Disaster**
  - St. John's wort was added to cyclosporin in a recent heart transplant recipient.
  - 3A4 and P-glycoprotein were induced.
  - The blood level of cyclosporin significantly decreased.
  - Rejection of the donor heart ensued.
  - Although PgP would not be involved, this DDI does occur with CBZ, PHT, or phenobarbital in the place of SJW and/or with tacrolimus in the place of cyclosporin.

3A4 Vignettes

- **Paranoia**
  - Phenytoin was added to quetiapine.
  - 3A4 was induced.
  - This led to a five-fold increase in the clearance of quetiapine with a marked decrease in the quetiapine blood level.
  - This led to a recurrence of paranoid delusions and inpatient hospitalization.

3A4 Vignettes

- **Unplanned Parenthood**
  - Carbamazepine was added to OCP.
  - 3A4 was induced.
  - The blood level of ethinyl estradiol (EE) significantly decreased.
  - Unintended pregnancy ensued.
  - This could just as easily have happened with the addition of phenytoin, phenobarbital, topiramate, or oxcarbazepine to EE.

3A4 Vignettes

- **Bitter Fruit**
  - Grapefruit juice was added to carbamazepine.
  - 3A4 and P-glycoprotein were inhibited.
  - The blood level of carbamazepine rose significantly.
  - Sedation, nausea, and tremor resulted.
  - Many hospitals have removed grapefruit juice from their menus due to these concerns.

3A4 Vignettes

- **Ataxic**
  - Erythromycin was added to carbamazepine.
  - 3A4 and P-glycoprotein were inhibited.
  - The blood level of carbamazepine (CBZ) rose significantly.
  - Sedation, ataxia, slurred speech, and jerking motions of arms resulted.
  - Although it was not a factor in this case, CBZ's induction of 3A4 could well have rendered the erythromycin ineffective.

3A4 Vignettes

- **Gradual Withdrawal**
  - Carbamazepine was added to chronic methadone.
  - 3A4 was induced.
  - The blood level of methadone decreased significantly (by about 60%).
  - Opioid withdrawal resulted.
  - This could also have occurred if PHT or phenobarbital was added to methadone.

3A4 Vignettes

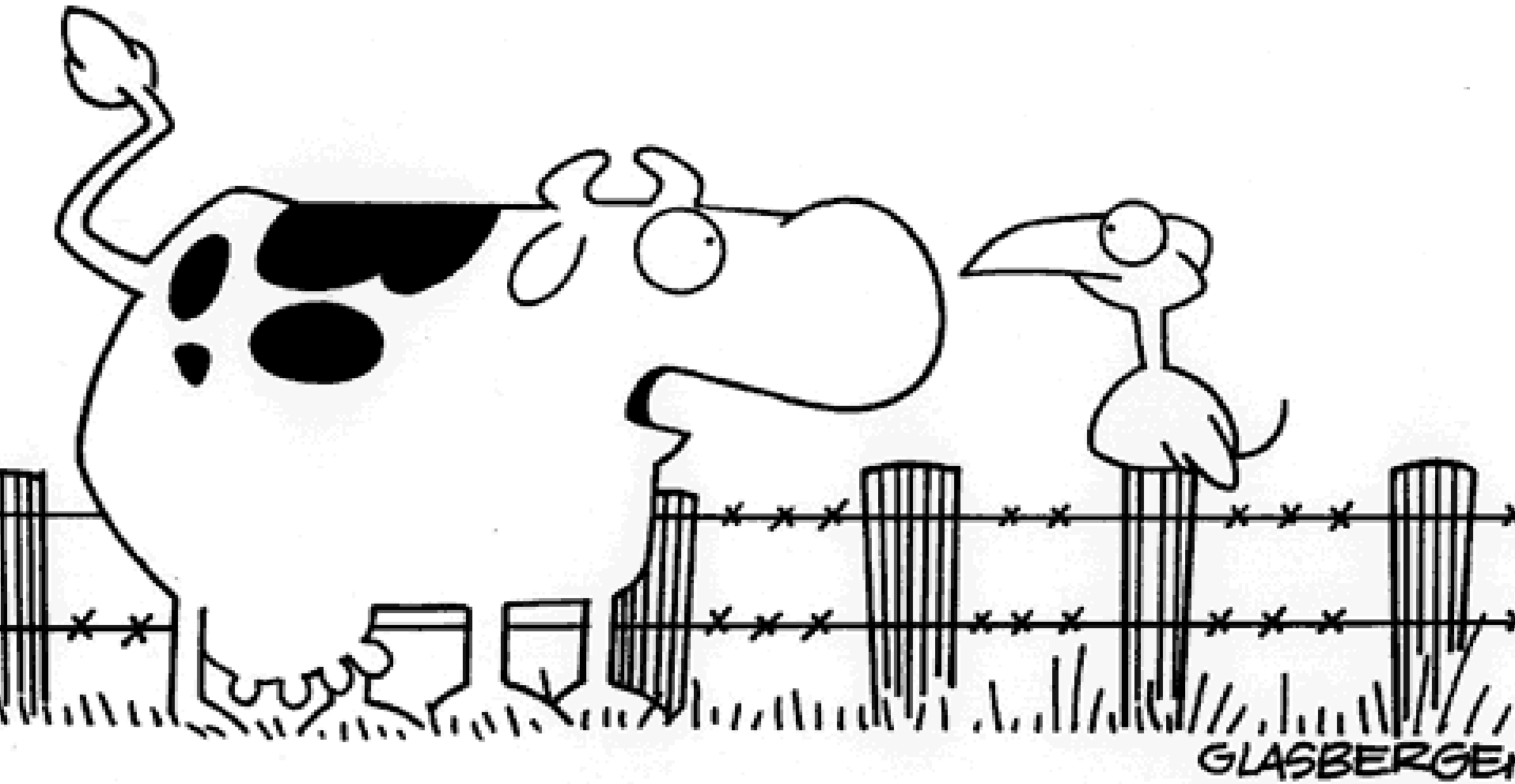
- **Inhibitor Induction**
  - St. John's Wort was added to indinavir.
  - 3A4 and P-glycoprotein were induced.
  - The blood level of indinavir decreased significantly.
  - An abrupt drop in the CD4 count resulted.
  - The success of HAART may be jeopardized by the addition of 3A4 inducers (CBZ, PHT, phenobarbital, etc.) if this effect is not anticipated and compensated for.

3A4 Vignettes

- **Gradual Withdrawal II**
  - Carbamazepine (CBZ) was added to alprazolam.
  - 3A4 was induced.
  - The blood level of alprazolam decreased significantly.
  - Again, this may occur with other 3A4 inducers (PHT, phenobarbital, etc.).

3A4 Vignettes

- **Cholesterol 451**
  - Phenytoin was added to atorvastatin.
  - 3A4 was induced.
  - The blood level of atorvastatin decreased significantly, leading to an increase in cholesterol level.



**"It's true, I did jump over the moon.
I had waaaaay too much coffee that day!"**

1A2 and Phase II Vignette

- **Conspiracy Theory**
  - Carbamazepine was added to olanzapine.
  - 1A2 and UGT 1A4 were induced.
  - The blood level of olanzapine decreased significantly (roughly 40%).
  - This resulted in a recurrence of psychotic symptoms.

2C9/2C19 Vignettes

- **Nystagmus**
  - Fluoxetine was added to phenytoin.
  - 2C9 and 2C19 (and PgP) were inhibited.
  - The phenytoin blood level significantly increased (by almost 100%), resulting in sedation, vertigo, and nystagnus.
  - This DDI is even more marked when fluvoxamine is added to PHT.

2C9/2C19 Vignettes

- **Double Fault**
  - Fluconazole was added to phenytoin (PHT)
  - 2C9 was inhibited.
  - The blood level of PHT rose significantly, producing nausea, slurred speech, and incoordination.
  - Fluconazole can also increase CBZ levels, although this is likely more attributable to its moderate inhibition of 3A4 than its potent inhibition of 2C9.

2C9/2C19 Vignettes

- **From Heartbreak to Heartburn**
  - Omeprazole was added to PHT.
  - 2C19 and P-glycoprotein were inhibited.
  - The blood level of PHT rose significantly, producing moderate PHT toxicity symptoms.

2C9/2C19 Vignettes

- **Just Desserts**
  - Valproate was added to glipizide.
  - 2C9 was inhibited.
  - The blood level of glipizide significantly increased.
  - This caused a decrease in the patient's serum glucose (51 mg/dL) with accompanying c/o dizziness, sweating, anxiety, and tachycardia (110 beats/min).

2C9/2C19 Vignettes

- **Sensitive**
  - Topiramate was added to phenytoin (PHT).
  - 2C19 was inhibited.
  - The blood level of PHT increased significantly (nearly 50%), leading to ataxia and drowsiness.
  - Although this did not come to light in this case, PHT's induction of phase II enzymes is likely responsible for the roughly 50% decreases in topiramate levels that occur with this combination.

2C9/2C19 Vignettes

- **Sensitive (cont.)**
  - This interactive pattern would also be seen when combining CBZ with PHT.
    - CBZ's inhibition of 2C19 would increase PHT levels.
    - PHT's induction of 3A4 and 2C8/9 would lower CBZ levels

2B6 Vignette

- **Optimization**
  - Phenytoin was added to the regimen of a patient with nonseminomatous testicular CA due to new onset seizures.
  - After two unsuccessful courses of chemotherapy, his third course, which included ifosfamide, was successful.
  - It is possible that PHT's induction of 2B6 led to more conversion of the pseudo-prodrug ifosfamide into its more active metabolite.

Non-P450 Vignette

- **Displaced**
  - Daily ASA was added to VPA
  - ASA both inhibited ß-oxidation and displaced VPA from plasma protein binding sites.
  - This led to only a modest increase in the total VPA level, but a roughly 150% increase in the free VPA level.
  - The patient experienced sudden onset of severe fatigue, sedation, and incoordination.

Complex P450 Vignettes

- **Vertigo**
  - CBZ was added to phenobarbital.
  - 1A2, 3A4, and 2C8/9 were induced by phenobarbital.
  - The level of CBZ dropped and the phenobarbital level remained unchanged.
  - The patient experienced mild sedation but significant vertigo.

Complex P450 Vignettes

- **Vertigo (cont.)**
  - These side-effects may have been attributable to a pharmacodynamic synergy, but another possibility is that phenobarbital's induction of 3A4 led to increased production of CBZ-10,11-epoxide.

Complex P450 Vignettes

- **Risky Regimen**
  - Carbamazepine was added to valproate.
  - CBZ induced phase II enzymes, leading to a roughly 60% decrease in VPA levels.
  - Also, CBZ's induction of (probably) 2C9 led to increased production of the hepatotoxic 4-ene-valproate metabolite.
  - VPA's inhibition of epoxide hydrolase led to increased levels of CBZ-10,11-epoxide.

Complex P450 Vignettes

- **Risky Regimen (cont.)**
  - Results:
    - Increased lethargy and irritability
    - Unsteady gait
    - First grand mal seizure in two years

Complex P450 Vignettes

- **High-Low**
  - Phenytoin was added to valproate
  - VPA both inhibited 2C9 and displaced PHT from plasma protein binding sites, thus increasing the total PHT level, with a disproportionate increase in the free concentration of PHT.

Complex P450 Vignettes

- **High-Low (cont.)**
  - PHT induced 2C9/19 and phase II enzymes, leading to:
    - A decrease in the VPA level, and
    - Increased production of the hepatotoxic 4-ene-valproate metabolite.

Complex P450 Vignettes

- **High-Low (cont.)**
  - Results:
    - Acutely, moderate sedation and "twitching eyeballs"
    - Two weeks later, a recurrence of mania
    - VPA level had declined from 105 µg/mL to 62 µg/mL, while the PHT level had increased from 17 µg/mL to 23 µg/mL (no free levels were obtained).

Phase II Vignettes

- **Contraceptive Convulsion**
  - An OCP was added to lamotrigine (which was being used as an anticonvulsant).
  - EE induced the production of glucuronidation enzyme 1A4, which metabolizes lamotrigine.
  - The blood level of lamotrigine decreased significantly, producing a grand mal seizure.
  - CBZ, PHT, phenobarbital, and oxcarbazepine (more weakly) also induce the metabolism of lamotrigine.

Phase II Vignettes

- **Rash Decision (I)**
  - This same patient doubled her lamotrigine dose to compensate for the EE, and remained seizure-free for years.
  - EE was then discontinued due to DVT.
  - A reversal of induction of glucuronidation enzyme 1A4 occurred.
  - This led to a rapid increase in the lamotrigine blood level, resulting in a drug rash.

Phase II Vignettes

- **Rash Decision(II)**
  - Divalproex was added to lamotrigine.
  - Glucuronidation enzyme 1A4 was inhibited.
  - The blood level of lamotrigine rose significantly and rapidly.
  - A drug rash ensued.
  - The addition of sertraline to lamotrigine can also double lamotrigine blood levels.

Lithium Vignette

- **The Tremulous Triathlete**
  - Indomethacin was added to lithium.
  - Inhibition of prostaglandin synthesis interfered with the excretion of lithium.
  - The lithium level increased significantly (about 50% in this case), resulting in polyuria, feeling “spacey”, and tremor.

Lithium DDIs

- Lithium levels are increased by:
  - NSAIDS except aspirin and sulindac
  - ACE inhibitors
  - Angiotensin II receptor antagonists
  - Thiazide and potassium-sparing diuretics (except amiloride)
  - Salt restriction

Lithium DDIs

- Lithium levels are decreased by:
  - Xanthines (incl. Caffeine) and osmotic diuretics
- Loop diuretics produce little or no change in lithium levels – inconsistent and unpredictable.

P-glycoprotein Vignettes

- **Stupor**
  - Omeprazole was added to carbamazepine.
  - Omeprazole inhibited P-glycoprotein function.
  - More absorption of carbamazepine resulted.
  - The blood level of carbamazepine increased significantly.
  - Frank delirium ensued.

P-glycoprotein Vignettes

- **Flaggelated**
  - Metronidazole was added to carbamazepine.
  - Indirect evidence leads me to believe that metronidazole is a P-glycoprotein inhibitor, which would thus yield increased absorption of carbamazepine.
  - In actuality, this combination did produce notable ataxia and delirium. A carbamazepine level was 27 micrograms/ml (therapeutic range = 4-12 micrograms/ml).

Take-home messages

- Preferentially use “safer” psychoactive agents.
  - Antidepressants
    - citalopram (Celexa)/escitalopram (Lexapro)
    - mirtazepine (Remeron)
    - venlafaxine (Effexor)
  - Anxiolytics
    - lorazepam (Ativan)
    - oxazepam (Serax)
    - clonazepam (Klonopin)

Take-home messages

- Antipsychotics
  - Beware of 1A2 effects, especially induction through smoking -- applies to typicals, olanzapine, and clozapine.
  - Beware of 3A4 inhibition and induction -- applies to aripiprazole, RISP, and quetiapine.
- "Mood stabilizers"
  - Many (but not all) of these are inducers, which can undermine the efficacy of other agents.

Take-home messages

- Preferentially use “safer” somatic agents.
  - pravastatin
  - azithromycin
  - H-2 blockers other than cimetidine.

Take home messages

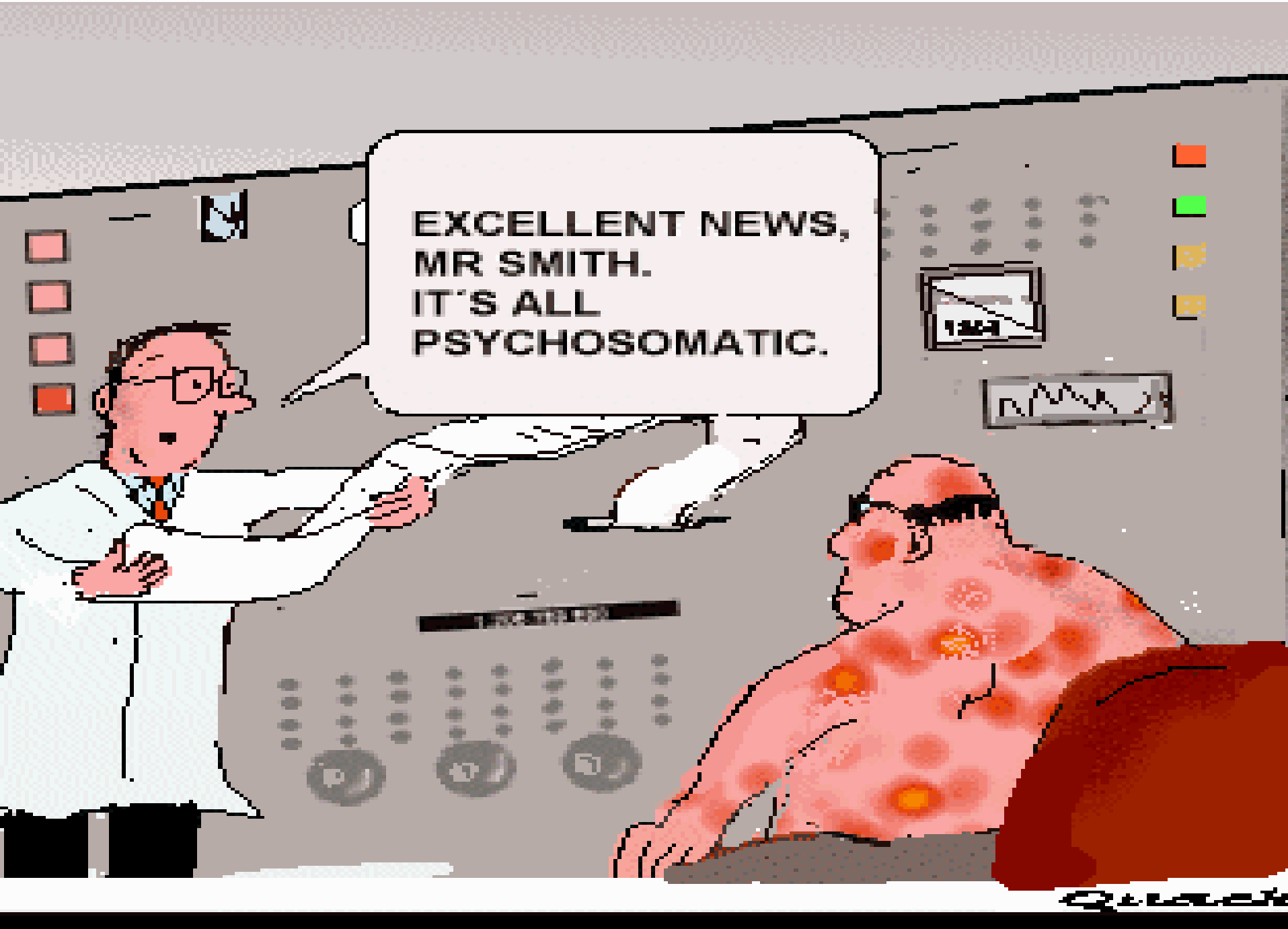
- Keep reliable references and other information sources close at hand.
  - Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins, by Kelly Cozza, M.D., Scott Armstrong, M.D., and Jessica Oesterheld, M.D.

Take home messages

- Drug Interactions Casebook: The Cytochrome P450 System and Beyond, by Neil Sandson, M.D.
- Dr. Oesterheld's site is at: http://www.mhc.com/Cytochromes
- Pub med is at: http://www.ncbi.nlm.nih.gov/pubmed

Take home messages

- Dr. Flockhart's site is at: www.drug-interactions.com (hyperlinks to pub med).
- The Physicians' Desk Reference online is at: www.pdr.net
- Existing drug interaction programs (ePocrates, ePocrates RxPro, MICROMEDEX, etc.) are not great (in my humble opinion), but they are a good deal better than nothing.


EXCELLENT NEWS, MR SMITH. IT'S ALL PSYCHOSOMATIC.

Take-home messages

- Most importantly, listen to the patient.
- Unless they are notoriously unreliable, their reports of difficulties are much more valuable and accurate than what little understanding we have about how our drugs work, how they fail, and how they interact with other drugs.

"...and, as you go out into the world, I predict that you will, gradually and imperceptibly, forget all you ever learned at this university."

Take-home messages

- Good luck, and may all your interactions be benign.