POLYPHARMACY : FOR AND AGAINST

NZMA GP CONFERENCE 2012
PSYCHOPHARMACOLOGY SERIES

- Guna Kanniah
- Waikato Hospital

POLYPHARMACY

FIVE REASONS FOR POLYPHARMACY

1. To treat a concomitant disorder
2. To treat an intervening phase of the illness
3. To treat an adverse effect
4. To boost or augment the desired effect
5. To speed the onset of the desired effect

- *J Prac Psych and Behav Hlth*. 1995

CRITERIA FOR RATIONAL COPHARMACY IN PSYCHIATRY

1. The combination has a positive effect on the pathophysiology or pathoetiology of the disorder

2. Combination is more effective, including more cost-effective, than monodrug therapy

3. The combination should not pose significantly greater safety or tolerability risks than monotherapy

• Drugs should not have narrow therapeutic indices

• Drugs should not have poor tolerability profiles

4. Drugs should not interact both pharmacokinetically and pharmacodynamically

CRITERIA FOR RATIONAL COPHARMACY IN PSYCHIATRY

5. Drugs with mechanisms of action that augments the desired response
6. Drugs with only one mechanism of action
7. Drugs should not have a broad-acting mechanism of action
8. Drugs should not have the same mechanism of action
9. Drugs should not have opposing mechanisms of action
10. Each drug should have simple metabolism
11. Each drug should have an intermediate half-life
12. Each drug should have linear pharmacokinetics

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 her 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 in 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
- Benzatropine 1 mg/day
- Ranitidine 300 mg/day

PSYCHIATRIST VISIT

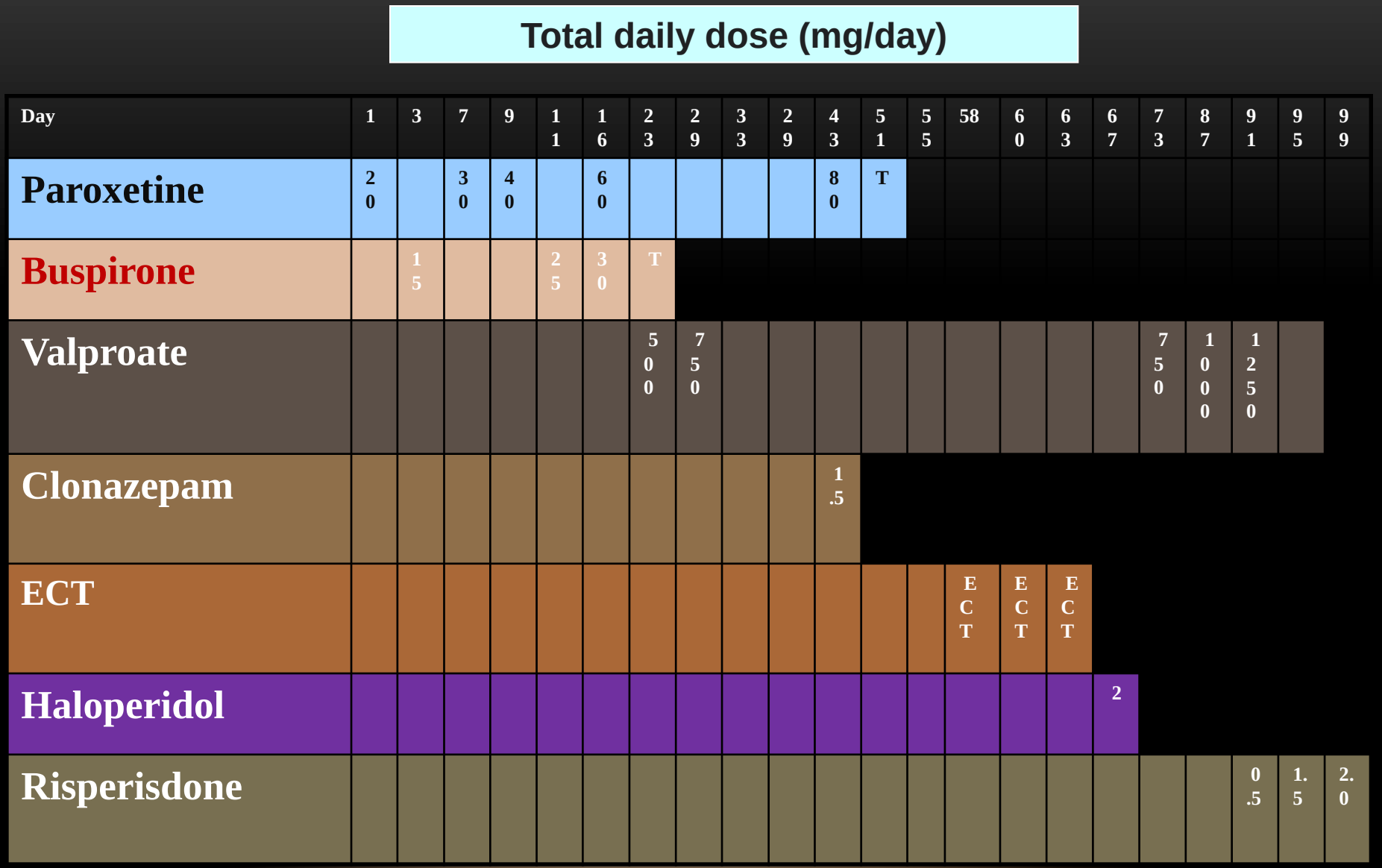
She came to community attention when her father sought a second opinion.

The interview was difficult because the patient appeared sedated unless she was actively engaged and prompted by the interviewer.

While her father was receptive to the recommendation to attempt to simplify the current regimen, the patient's mother was convinced that her daughter would significantly deteriorate if any of the medications were stopped or even reduced

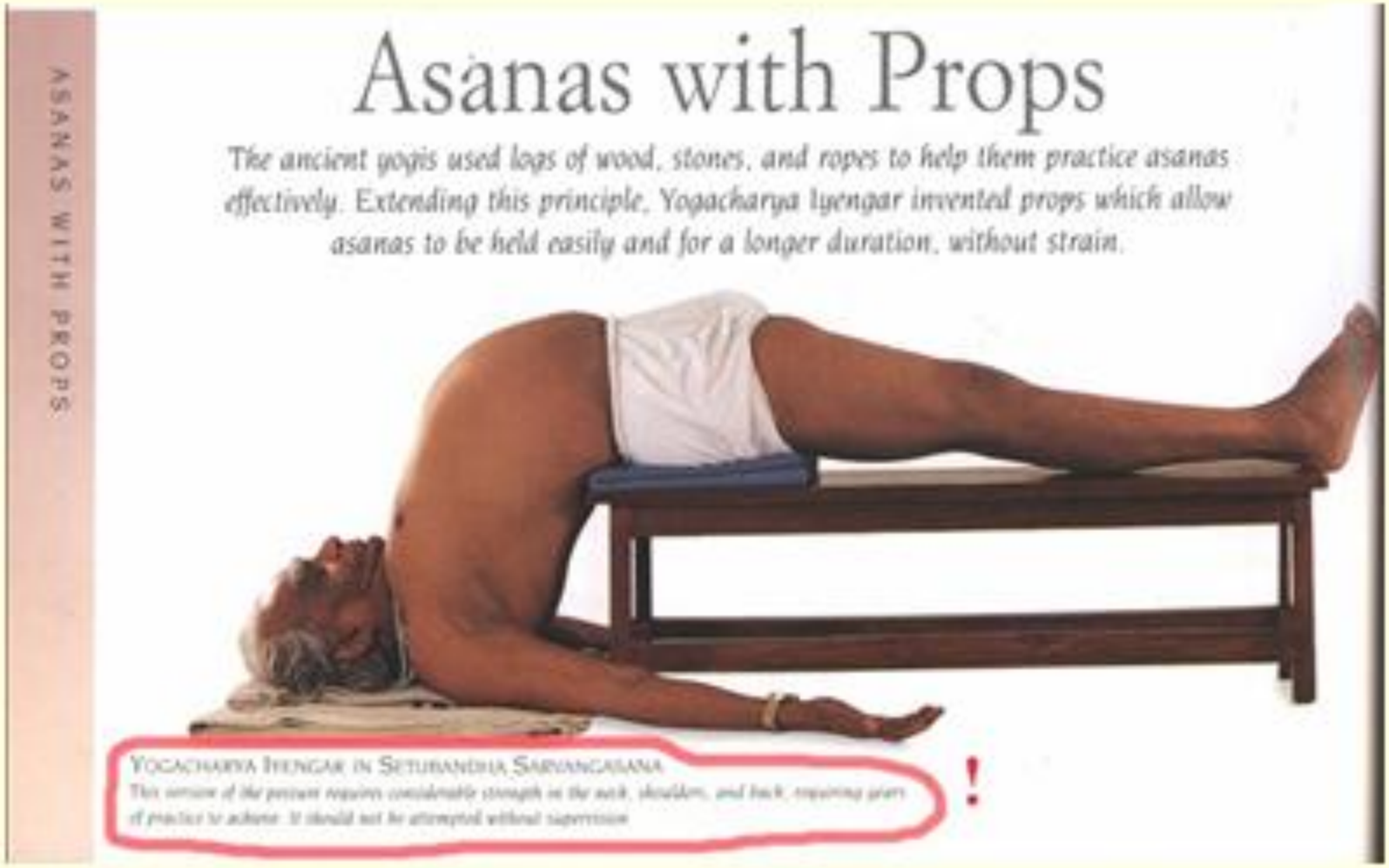
MEDICATION HISTORY

- There were no comorbid medical problems.
- Plasma drug levels of the first five drugs listed above were consistent with the prescribed doses.
- The longitudinal course of her prior treatment was plotted based on her medical records (Table 1).
- Only the first 3 months are shown for brevity's sake, and they sufficiently illustrate the major points



Longitudinal course of treatment

Yoga for Mental Health



ALTERNATIVE YOGA

- Next slide

DIFFERENT MEANS ……

……SIMILAR OUTCOME!!!

TREATMENT REGIMEN

Majority, might agree with the decision to immediately initiate an empirical trial, given the safety and tolerability of SSRI's

However, an empirical trial requires discipline and patience.

Neither was obvious in the management of this case.

STARTING ON SSRI' S

- SSRI's have a flat dose-response curve,
- On average, there is no advantage to raising the dose above the usually effective dose in most, but not all, patients.
- Flat DR curve due to single mechanism of action
- Higher does produce an increase in inhibition but more serotonin mediated adverse effects rather than efficacy
- Exceptions – Inter-individual differences in clearance and pharmacodynamic sensitivity

Day	1	3	7	9	11	16	23	29	33	29	43	51	55	58	60	63	67	73	87	91	95	99
Paroxetine	20		30	40		60					80	T										

SSRI DOSE ESCALATION

This patient did not receive an adequate trial of the usually effective dose of paroxetine, 20 mg/day.

She was on this dose only 6 days before it was escalated to 30 mg/day.

Within 2 weeks of starting this drug, she was on **60 mg/day**, which is above the maximum recommended dose in adults.

This patient was kept on 60 mg/day for 3 weeks and then the dose was escalated to 80 mg/day.

SSRIS CONT…

- The recommended maximum daily dose for adolescent has not been definitively established.
- Hence, it would be prudent to use caution when exceeding the dosing guidelines for adults, even though adolescents conceivably may clear the drug faster than adults and thus could need higher doses.
- But need to use TDM to support higher doses

SSRI'S

- Given the pharmacology of SSRIs, the rationale behind the use of doses well above the usually recommended maximum is suspect

SSRI ADVERSE EFFECTS

SSRIs produce a number of dose dependent adverse effects that could mimic worsening of the underlying illness.

These include agitation, restlessness, anorexia, insomnia, and daytime fatigue.

This patient had reported these symptoms as the dose of paroxetine was increased.

The question is whether they occurred *despite* the medication or *because of* the medication.

AUGMENTATION WITH BUSPIRONE

This patient's trial of paroxetine is further complicated by the rapid addition and subsequent periodic dose escalation of buspirone, another serotonin active medication.

The addition of this drug raises the possibility of clinically significant pharmacokinetic and pharmacodynamic drug-drug interactions.

SSRI INTERACTION

Paroxetine and buspirone act on different but related central serotonin (5-HT) mechanisms, paroxetine as an **inhibitor** of the serotonin uptake pump and

Buspirone as a **partial agonist** of the 5-HT1a receptor.

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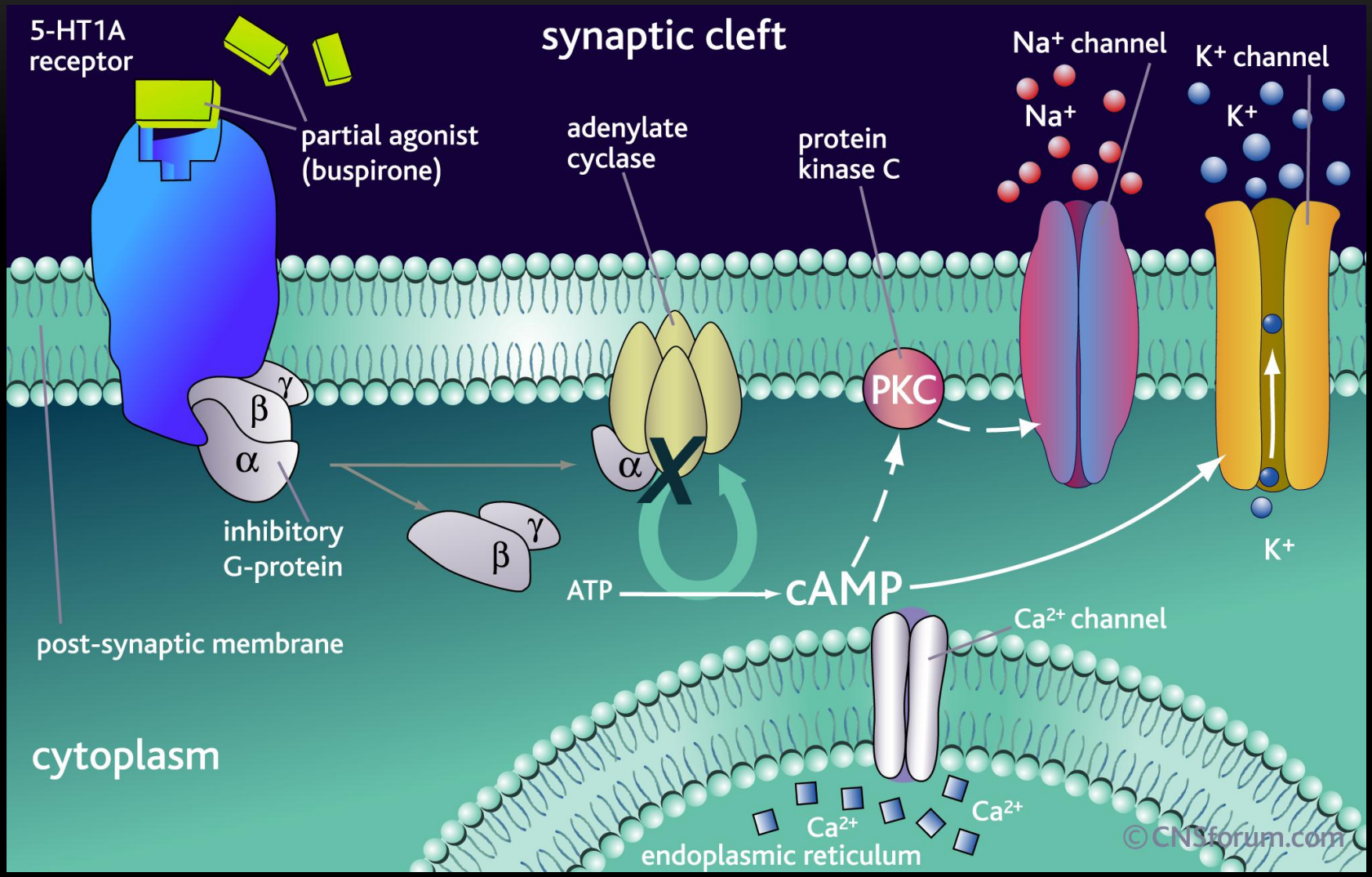
This receptor presynaptically regulates serotonin cell firing and postsynaptically mediates serotonergic effects in specific terminal fields.

Blockade of the presynaptic 5-HT1a receptor can produce a loss of the normal feedback mechanism and hence can result in overactivity of the serotonin system

BUSPIRONE PHARMACOLOGY

made more complicated by the fact that buspirone is converted to a centrally active metabolite, 1-phenyl-piperazine (1-PP).

This metabolite, like buspirone, acts at the 5-HT1a receptor but is even more potent as an alpha-2 adrenergic receptor blocker


5-HT1A
receptor
partial agonist
(buspirone)
synaptic cleft
adenylate
cyclase
protein
kinase C
Na+ channel
Na+
K+ channel
K+
PKC
γ
β
α
α
X
inhibitory
G-protein
γ
β
ATP
cAMP
K+
post-synaptic membrane
Ca2+ channel
cytoplasm
Ca2+
Ca2+
endoplasmic reticulum
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BUSPIRONE METABOLITE PHARMACOLOGY

The effect of 1-PP was pharmacokinetically potentiated in this case because it is virtually (if not exclusively) dependent on CYP 2D6 for its clearance.

Paroxetine at 20 mg/day produces 85% inhibition of CYP 2D6.

At the doses used in this case, CYP 2D6 was most likely fully inhibited, leading to as much as a 10-fold increase in usual 1-PP accumulation

PAROXETINE–BUSPIRONE INTERACTION

The goal of using buspirone in combination with an SSRI is to produce a drug-drug interaction that will be therapeutic for the patient.

The clinician needs to be aware that pharmacologically the net result is to increase or decrease the effect of the first drug by altering its pharmacodynamics or pharmacokinetics.

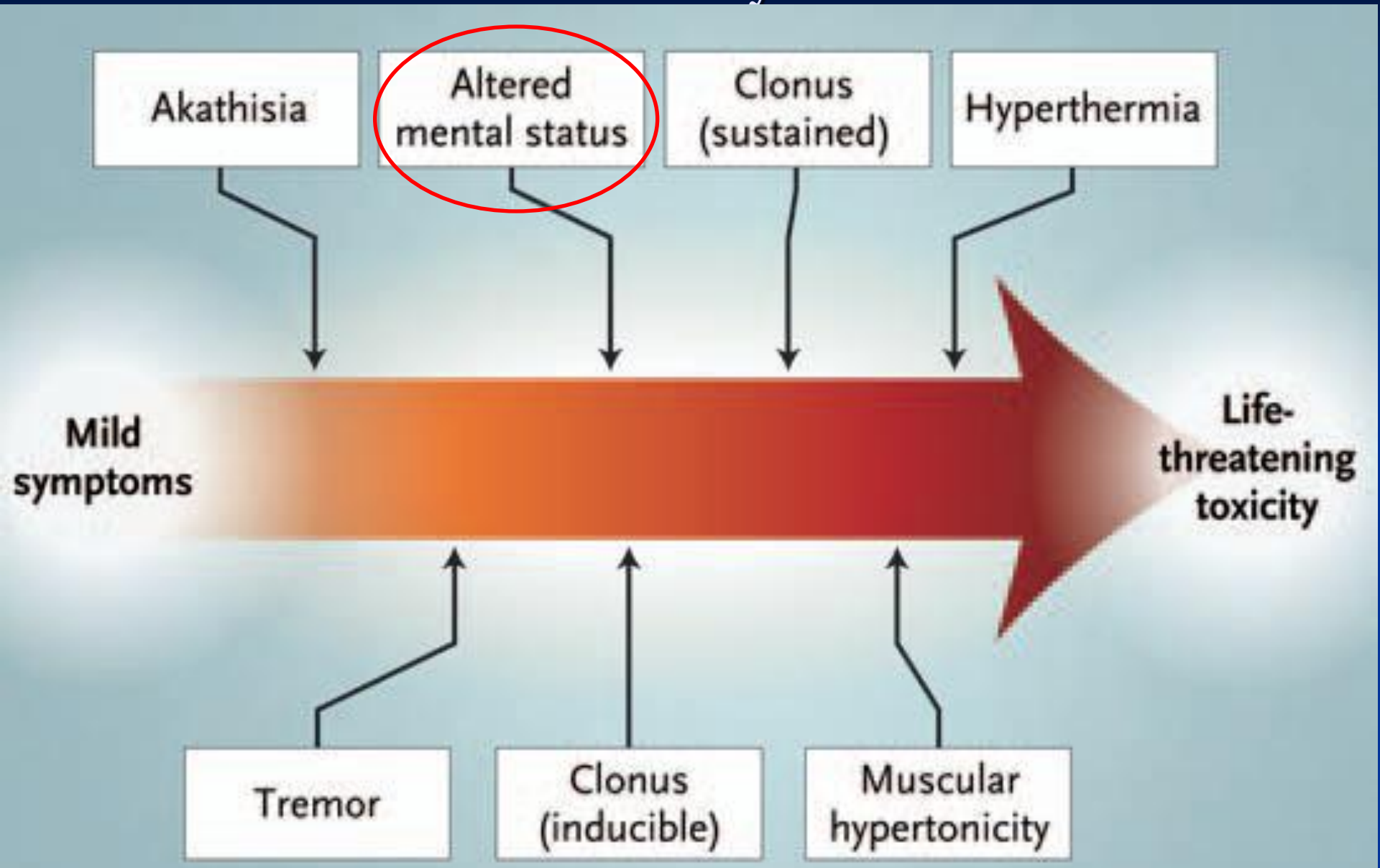
POTENTIATION AND CONSEQUENCES

In this case, the patient had substantial serotonin uptake inhibition to which was added the effects of buspirone and 1-PP on both 5-HT1a and alpha-2 adrenergic receptors.

Such a combination of effects could potentially cause a partial central serotonin syndrome, which can present as either delirium or mania.

Consistent with this possibility this patient developed signs of mania on day 23 of treatment.

Spectrum of clinical findings in Serotonin syndrome



FURTHER TREATMENT ADJUSTMENTS

On day 23,

the decision was made to discontinue buspirone and add valproate ……

for what was interpreted to be emerging mania.

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RATIONALE

This series of events is consistent with the fact that adverse effects due to psychotropic medications or combinations of medications can mimic psychiatric symptomatology and can result in more medications being added rather than in the treatment regimen being simplified.

This explanation is plausible in this case given the course of events

FURTHER ADDITIONS

On day 43,

paroxetine was increased to 80 mg/day, which is four times the usually effective dose and well above the maximum recommended dose for adults.

Clonazepam was also added on day 43 because of increasing agitation, which is a dose-dependent adverse effect of SSRIs.

Again, the clinician may have been adding a medication to treat an adverse effect resulting from excessive serotonin uptake inhibition.

Consistent with that explanation, the agitation worsened after the paroxetine dose was increased, causing the clinician to “taper” the patient from 80 mg/day to 0 mg/day over 4 days.

Withdrawal has been reported following the abrupt discontinuation of SSRIs.

The relative risk and the severity of such withdrawal is a function of the daily dose and the half-life of the SSRI.

Withdrawal can cause a number of symptoms that can mimic a worsening of the patient's psychiatric status, including

- agitation,
- irritability,
- aggression, tremulousness,
- sleep disturbances, nightmares,
- difficulties concentrating,
- "racing thoughts," and
- confusion

SSRI WITHDRAWAL SYNDROME

This patient developed most of these symptoms during the "taper," which were interpreted as further evidence that the patient was becoming "manic."

For that reason, valproate and clonazepam were abruptly discontinued on day 55 and the patient was given three electroconvulsive treatments (ECT).

The effects of these treatments

were thus likely superimposed on a state of SSRI withdrawal, which typically takes at least 1–2 weeks to resolve on its own.

The ECT treatments were discontinued because the patient became confused and psychotic.

FURTHER MODIFICATIONS OF DRUG REGIMEN

That further reinforced the treating psychiatrist's opinion

that the patient was manic.

Haloperidol was therefore started.

Subsequently, valproate and clonazepam were reinstituted, and the patient was switched from haloperidol to risperidone.

She eventually ended up on the regimen outlined at the beginning of this column.

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PERSPECTIVES

Conceivably, *all of them* were needed exactly as prescribed— but it was also conceivable that *none of them* was needed.

Whenever possible, we prefer to initiate treatment with adequate monotherapy trials to determine what effect a specific medication and ideally a specific mechanism of action will produce in the patient:

beneficial response,

an adverse response,

or no effect.

DOWN THE ROAD …..

After 3 months, this

patient was on

lithium 900 mg/day and

fluoxetine 20 mg/day

with the only apparent consequence being an appreciable improvement in her functional status

DISCUSSION & RECOMMENDATIONS

psychiatric illnesses are cyclic

risk for relapse after a medication is discontinued,

caution in management follow-up.

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RECOMMENDATIONS

Maintaining the patient on this regimen for 3 months to obtain a new baseline.

If no return of symptomatology occurs,

continue a gradual taper of one of these two remaining medications.

The goal of treatment is try with the minimum number of medications necessary to achieve maximum functional status.

LEARNING CURVE

Clinicians be aware of the following considerations when embarking on the use of multiple medications:

1. Potential for drugs to interact pharmacodynamically and/or pharmacokinetically to alter the expected effect or response,

2. Need to give disciplined trials of medications, ideally in isolation, before increasing the dose too quickly or too much or before adding other agents,

LEARNING CURVE

3. Need to consider that deterioration may be *because of* the drug therapy rather than *in spite of* it,

4. Need to realize that *stopping* medication is doing something as opposed to thinking that one is only doing something when one is *adding* medications,

5. Need to stop psychiatric medications properly, which often requires a gradual taper; otherwise withdrawal effects can mimic worsening of the underlying illness.

ITS WORTH INVESTIGATING THE RISKS

THANK YOU