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Common Problems with Psychotropics in Primary Care - Concurrent Workshop Repeated

Sunday, 18 August 2013	Start 8:30am	Duration: 55mins	Monet
	Start 9:25am	Duration: 55mins	Monet

Common Problems with Psychotropic Drugs

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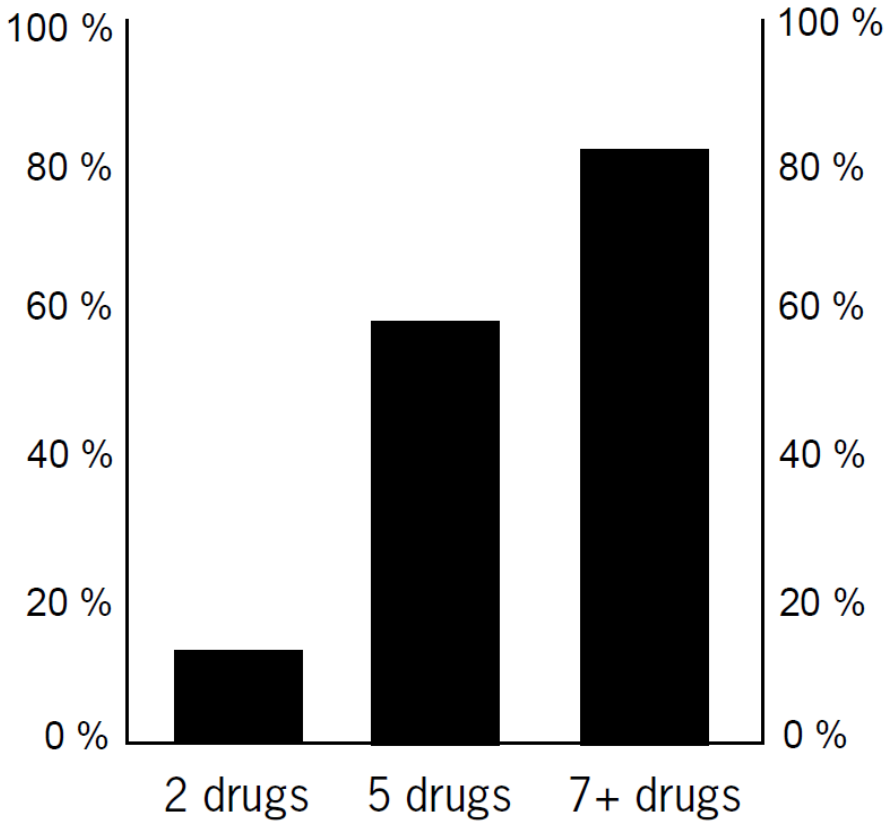
Abbreviations

ACh	Anticholinergic
BIBA	Brought In By Ambulance
BIBP	Brought In By Police
CMHT	Community Mental Health Team
CNS	Central Nervous System
MHS	Mental Health Service
nAChR	Nicotinic AcetylCholine Receptor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	TriCyclic Antidepressant
	Red Flag for Caution

Polypharmacy



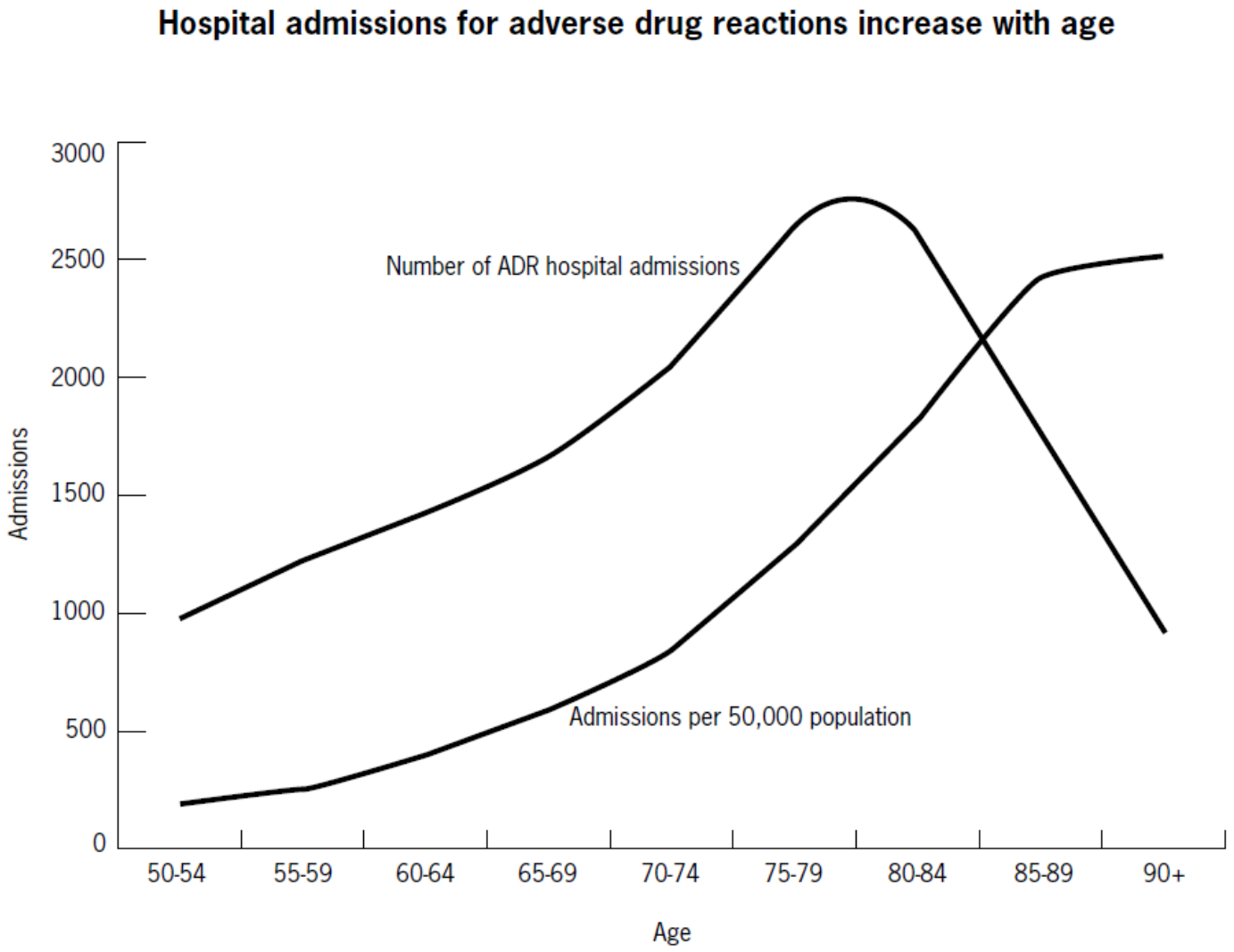
The risk of an adverse drug event is estimated at:

- 13% for two drugs
- 58% for five drugs
- 82% for seven or more

Fulton MM, Allen ER. Polypharmacy in the elderly: A Literature Review. J Amer Acad Nurse Pract. 2005;17(4):123-131.

Bjerrum L, J. Sogaard, J. Hallas, J. Kragstrup. Polypharmacy: correlations with sex, age and drug regimen, Eur J Clin Pharmacol. 1998;54(3):197–202.

A Particular Problem in Older Adults



BPAC Polypharmacy 2005

Polypharmacy

- Not terribly uncommon when discharged back to General Practice

- Ascertain or develop a plan for medications:
  - Benzodiazepines when to reduce and discontinue?
  - Zopiclone when to discontinue?
  - Quetiapine add-on when to reduce and discontinue?
  - Incomplete cross titration?

- If the plan is to continue with the polypharmacy:
  - When will it be reviewed?
  - What monitoring is required?

Chopping & Changing

- Why change?
  - Patient initiated?
  - Is the current regimen so ineffective or intolerable?
- Is the change in line with the plan - CMHT?
- What is the level of risk with this person?
  - What happens when they decompensate?
  - History of suicidal or homicidal ideation or action?

- Have we been here before with this person?
  - What is the relevant history?
- How fast is change required?
- What is the risk?
- Require a plan or monitoring in case of poor result?

Chopping & Changing: To Do List

Firstly:

- Check the plan - CMHT
- Check the history
- Check the drugs:
  - Any likely discontinuation effects
  - Mechanism of change
- Need a pharmacist?

Then:

- Discuss with the patient including;
  - The schedule
  - Expected clinical and adverse effects

Chopping Mechanism

- Firstly: Is it wise to discontinue this medication?
- Best to discontinue any psychotropic medication slowly
- If there's no rush allow one to two week intervals as titrate down in smallest dose or half-tablet steps, for example:
  - Fluoxetine, citalopram, paroxetine = 10mg steps
  - Escitalopram = 5mg steps
  - Sertraline = 25mg steps
  - Venlafaxine = 37.5mg
- Go even slower in OCD maybe four week intervals
- Long-term benzodiazepines are a special case and may require much longer to discontinue

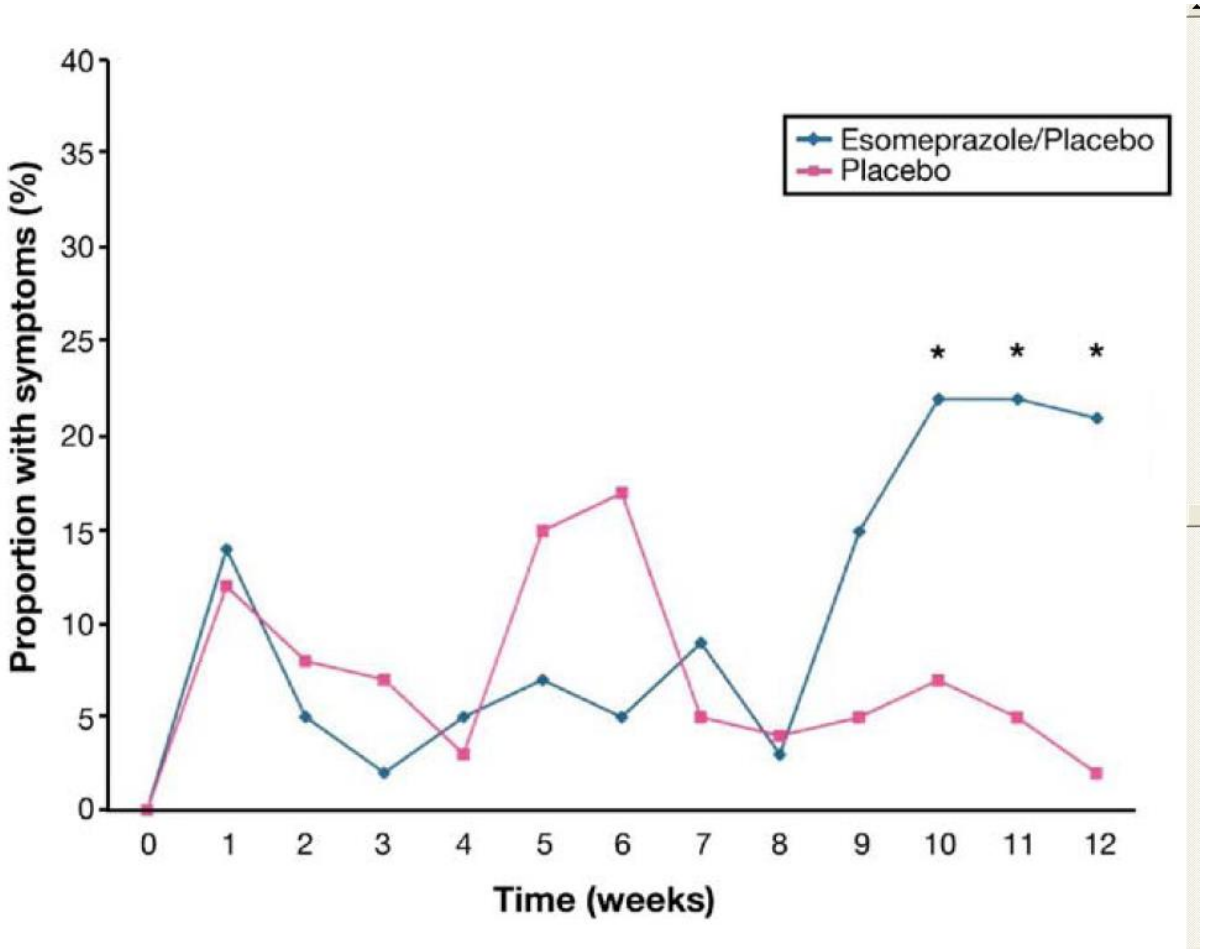
Changing Mechanism

- Best to manage change slowly
- Be mindful of the loss of clinical effect from the first agent and slow onset of clinical effect from the second
- Allow at least four weeks if there is no rush
- **Cross titration** works very well
  - Antipsychotics: depends on age, illness, severity of illness and medication history
  - Mood stabilisers: essential
  - Antidepressants: with care in general
    - extra care with fluoxetine
    - and not at all with MAOI

Chopping & Changing

- Discontinuation Effects
  - Rebound Insomnia when discontinue sedative drugs
    - Antihistaminic drugs
    - Sedative/hypnotics
  - Antidepressant Discontinuation Syndrome
  - Cholinergic Rebound
- Antipsychotic withdrawal
  - Cross titration
- Switching Antidepressants

Rebound Acid Hypersecretion (RAHS)



Score >2 indicating at least mild discomfort measure by GSRS
The PPI/placebo group received esomeprazole 40mg daily in weeks 1-8, followed by placebo in weeks 9-12. Placebo group received placebo tablets in weeks 1-12. Reimer, et al. Gastroenterology 2009;137:80-87

Antidepressant Discontinuation Syndromes

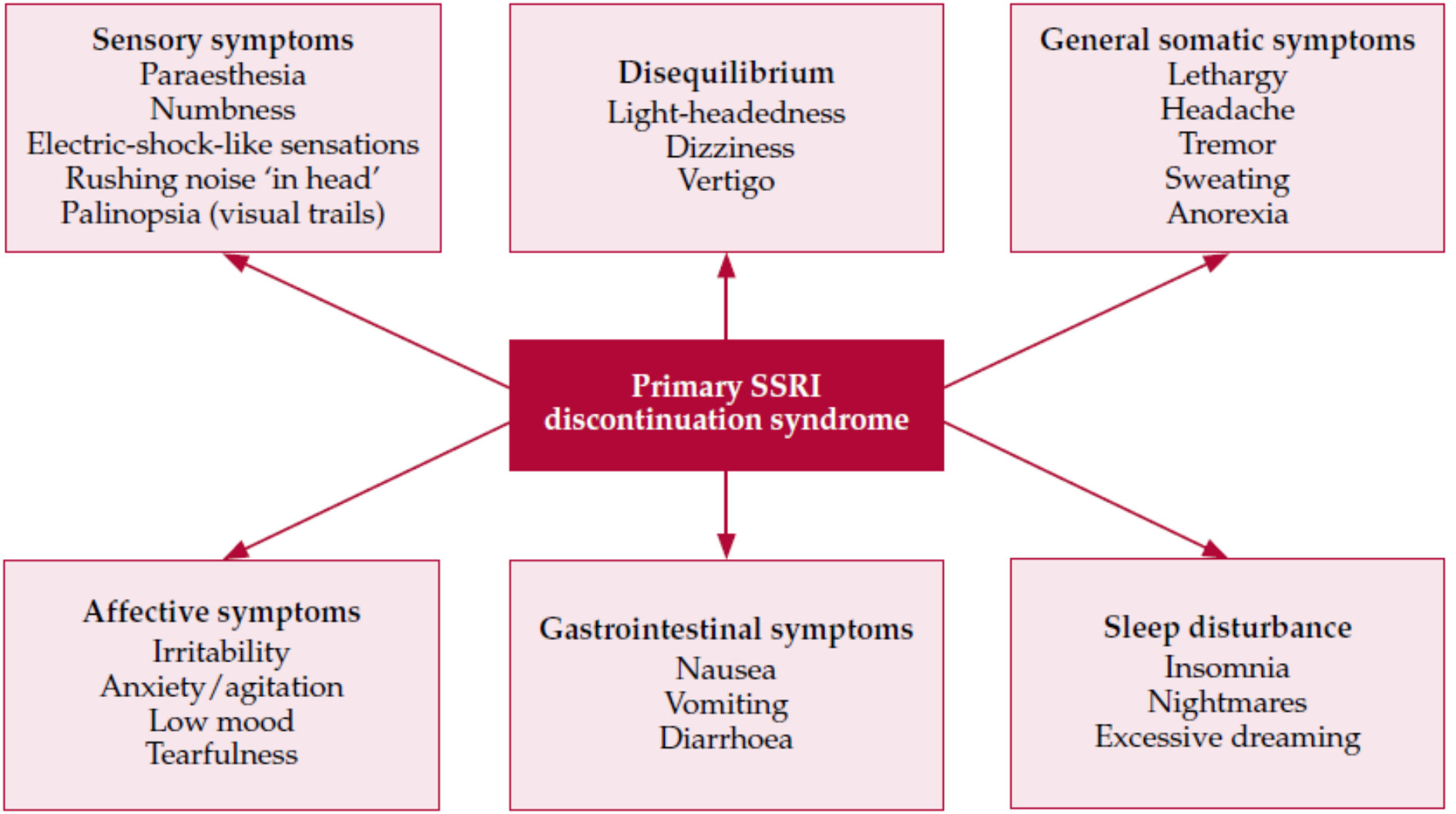
- Often described as a withdrawal syndrome - it is not
- Occurs with antidepressants from all major classes
  - Most common with paroxetine and venlafaxine
- Reactions are usually mild, but can be severe.
  - Many symptoms are physical not psychological
  - Case reports describe inappropriate investigations
  - Often neglected in medical textbooks
  - Risk of misdiagnosis
- The abrupt onset of characteristic symptoms within 48 hours of missed antidepressant or dose reduction, e.g.:
  - Dizziness, nausea, buzzing noise in the head, shock-like sensations (brain zaps)
- Easily avoided or minimised by titrating off slowly

Differential

- A discontinuation syndrome must be distinguished from a recurrence (a new episode) of depression.
- If there are doubts and symptoms are not severe, then the clinician and patient can monitor the symptoms and reserve a definitive diagnosis to a later date.
- If adopting this approach the clinician should give a full explanation to the patient.
- A sudden onset of symptoms with spontaneous resolution within about ten days is the norm with discontinuation reactions
- Depressive illness onset more gradual worsens with time and is more persistent: 2-weeks of symptoms required for diagnosis of a major depressive episode in DSM–IV

Haddad & Anderson. *Journal of Psychopharmacology,* ***15, 139–141***

Common key symptoms of primary SSRI discontinuation syndrome. Note; many others are reported and patients differ in the number and combination of symptoms manifested



Haddad & Anderson. *Journal of Psychopharmacology,* ***15, 139–141***

The Case of Miss A

- Miss A, 23 year old, Maori mother of two, unemployed
- Previously bubbly, now tired and fatigued
- Diagnosed with depression; paroxetine commenced
- Two months later presents with flu-like symptoms, dizziness on turning her head, and says she gets little electric shocks all the time.
- You learn Miss A just returned from a two-week holiday and she ran out of medication, missed three days
- This presentation sounds like antidepressant withdrawal
  - Should resolve on recommencing paroxetine
  - Reassure that the antidepressant is not addictive
  - To see doctor if symptoms do not resolve
- May actually have a cold or flu as well

Venlafaxine of High Risk

- Symptoms of discontinuation are similar to other antidepressants including:
  - irritability, restlessness, headache, nausea, fatigue, excessive sweating, dysphoria, tremor, vertigo, irregularities in blood pressure, dizziness, visual and auditory hallucinations, feelings of abdominal distension, and paresthesia.
  - Non-specific mental symptoms may include impaired concentration, intense and unpleasant or bizarre dreams, delirium, cataplexy, agitation, hostility, and worsening of depressive symptoms
  - Shock-like sensations or brain zaps

Potential for Misdiagnosis

1. As an adverse effect of new medication
   - e.g.; when switching antidepressants
2. As a recurrence of underlying illness
   - e.g.; legitimate discontinuation becomes unnecessary reinstatement and more negative prognosis
3. As discontinuation mania or hypomania
   - Rare, may lead to erroneous diagnosis of bipolar disorder with commencement of mood-stabilisers
4. As a physical disorder
   - Unnecessary investigations and stress for patient and family
5. As failure to respond to treatment
   - Covert non-adherence taken as worsening of illness
   - Then dose increased, augmented, or antidepressant switched...

Haddad & Anderson. *Advances in Psychiatric Treatment (2007), vol. 13, 447–457*
doi: 10.1192/apt.bp.105.001966

Two More Cases

- Both presented with rapid onset of disabling neurological symptoms, marked weakness, neither could walk unaided and required assistance with bathing and eating
- Both cases no relevant medical history
- In both cases the patient and a relative suspected a stroke and arranged emergency medical consultation
- Case 1: also dysarthria & palinopsia
  - Promptly diagnosed and resolved; reinstatement + slow titration
- Case 2: also numbness and shocks
  - Consulted widely: GP, CPN, Psychiatrist, ER Dr, Neurologist
  - Multiple investigations: including CT Head, EEG
  - Symptoms persisted beyond eight weeks before diagnosed

Haddad, P. M, et al.(2001) Antidepressant discontinuation symptoms presenting as ‘stroke’. *Journal of Psychopharmacology,* ***15, 139–141.***

Managing Antidepressant Discontinuation

- Titrate off slowly; reduce dose every 7 to 14 days, some people tolerate bigger steps every 5 days:
  - TCA: reduce in 50mg steps to 50-75mg daily then 25mg steps
  - SSRI: reduce by 20mg steps to 20mg daily then to 10mg daily then off, with paroxetine may need to finish with 10mg alternate days then off
  - Sertraline reduce by 50mg steps
  - Venlafaxine reduction in 75mg steps may not be tolerated, use 37.5mg steps until off
  - Mirtazapine reduce in 15mg steps to 15mg then off
- Some authors suggest switch other SSRI or Venlafaxine to fluoxetine or citalopram and wean off – Caution

Discontinuation: Cholinergic Rebound

Neurologic	Akathisia, delirium, disorientation, dizziness, vertigo, dyskinesia, tremor, memory impairment
Sleep Disorders	Insomnia; excessive, vivid and early-onset dreaming; nightmares; sleep apnoea
Psychiatric	Anxiety, panic, apathy, depersonalisation, depression, irritability, hypomania, mania
Medical	Gastrointestinal; abdominal pain, anorexia, diarrhoea, dry mouth, nausea, vomiting, salivation Flu-like symptoms; headache, malaise, myalgia, sweating, weakness Palpitations, tachycardia Autonomic dysfunction; increased temperature, piloerection

Cholinergic Rebound: Anticholinergic Drugs

- **Tricyclic Antidepressants ← all of them**

- Benztropine, clozapine, duloxetine, hydroxyzine, maprotiline, phenobarbitone, chlorpromazine, olanzapine, orphenadrine, paroxetine, pimozide, prochlorperazine, procyclidine , promethazine, thioridazine, thiothixene
- Oxybutinin, tolteridine
- Other less likely; brompheniramine, codeine, cyclizine, digoxin, doxylamine, frusemide, hyoscine, ipratropium, isosorbide nitrates, loratadine, nifedipine, prednisolone, theophylline

Has the Potential to Precipitate Illness

- Possibly a factor when people who discontinue clozapine abruptly decompensate quickly
- When gastrointestinal, neurological, anxiety or depressive symptoms present with acute onset in a person with previous response to treatment

Potential for Misdiagnosis: Same as Before

1. As an adverse effect of new medication
   - e.g.; when switching antidepressants
2. As a recurrence of underlying illness
   - e.g.; legitimate discontinuation becomes unnecessary reinstatement and more negative prognosis
3. As discontinuation mania or hypomania
   - Rare, may lead to erroneous diagnosis of bipolar disorder with commencement of mood-stabilisers
4. As a physical disorder
   - Unnecessary investigations and stress for patient and family
5. As failure to respond to treatment
   - Covert non-adherence taken as worsening of illness
   - Then dose increased, augmented, or antidepressant switched...

Cholinergic Rebound - Management

- If symptoms are mild withhold treatment, restart the drug and slowly taper the dose over weeks

OR

- Withhold the drug and add an anticholinergic agent if slow titration is not possible
  - Benztropine if CNS symptoms are present
  - Hyoscine-n-butylbromide if only gastrointestinal symptoms present

Acetylcholine

- Acetylcholine helps with memory, learning, and concentration.
- It also helps control the functioning of the heart, blood vessels, airways, and organs of the urinary and digestive tracts.
- So drugs with anticholinergic effects can disrupt the normal functioning of these organs.
- Dysregulation of the cholinergic system may also contribute to the etiology of major depressive disorder

Anticholinergic Effects

Acute Effects:

- Blurred vision
- Constipation
- Dry mouth
- Difficulty starting urination
- Urinary retention
- Sedation
- Sweating inhibited - hyperthermia
- CNS Changes:
  - Learning & memory
  - Exacerbate positive symptoms of schizophrenia
  - Toxic confusional state

Chronic Effects

- Constipation & urinary effects
- Abuse potential due to mild euphoriant effects
- Impairs cognition
- May exacerbate or unmask tardive dyskinesia
- Reduced action of typical antipsychotics through liver enzyme induction

Anticholinergics in Older People

Older people are more likely to experience anticholinergic effects because as people age:

- the body produces less acetylcholine
- cells in many parts of the body, such as the digestive tract, have fewer sites where acetylcholine can bind
- Thus, the acetylcholine produced is less likely to have an effect...
- and the effect of anticholinergic drugs is greater

Anticholinergics in Older People

- The elderly frequently use ACH drugs and
- Are expected to be particularly sensitive to central ACH side effects
- ACH drugs are strongly suspected to have negative effects on cognition as well as on behaviour in older persons
- Although further studies are needed to unequivocally prove the link

Consider the *Anticholinergic Load* of several drugs with varying anticholinergic potency add up to adverse effects

Cancelli & Gigli. Drugs with anticholinergic properties: cognitive and neuropsychiatric side-effects in elderly patientsNeurol Sci (2009) 30:87–92
DOI 10.1007/s10072-009-0033-y

- Results suggest that serum anticholinergic activity can be detected in most older persons in the community and confirm that even low serum anticholinergic activity is associated with cognitive impairment, although most apparent with high potency antimuscarinic agents.

Clinical studies show that anticholinergic agents may produce cognitive deficits in young adults similar to the cognitive deficits seen in elderly people.

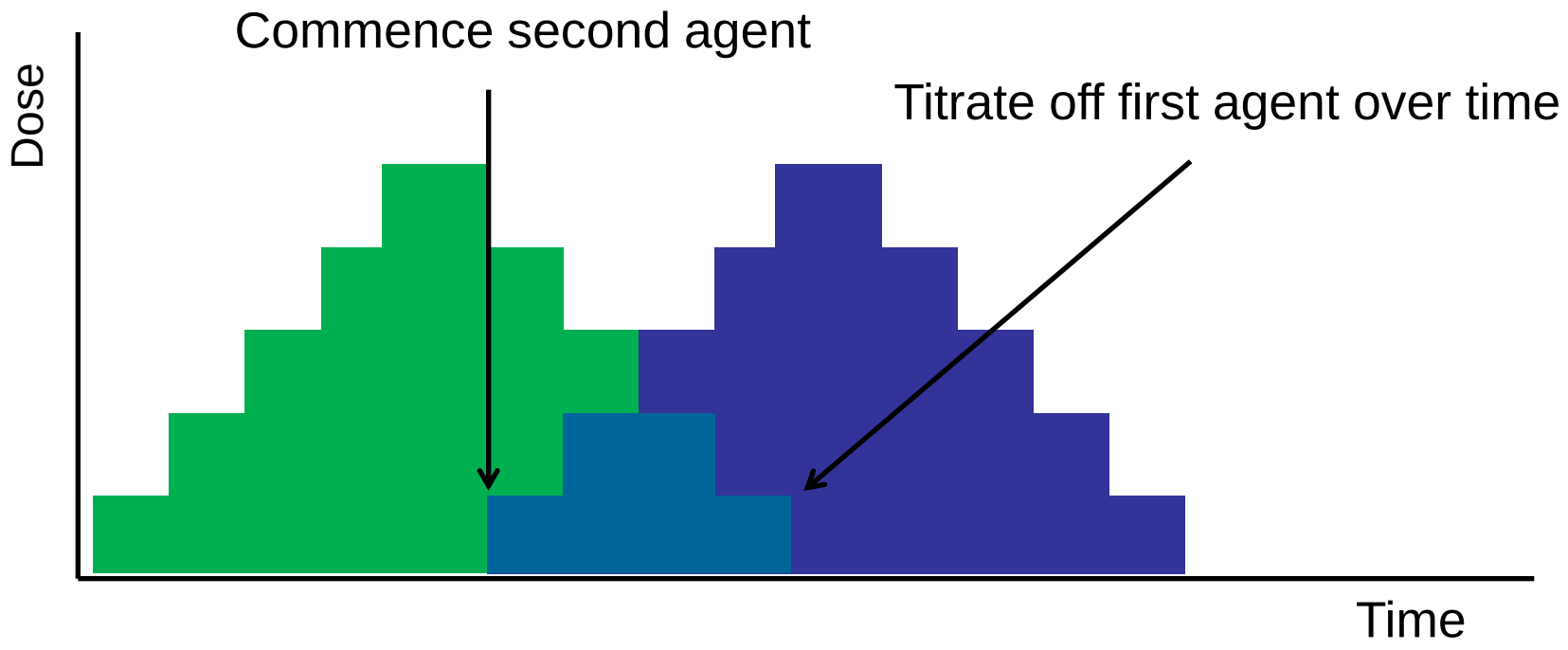
Campbell, et al. Clinical Interventions in Aging 2009:4 225–233
Fox, et al. Journal of the American Geriatrics Society 2011.

Antipsychotic Withdrawal

- Withdrawal symptoms from antipsychotics may emerge during dosage reduction and discontinuation.
- Withdrawal symptoms can include:
  - nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia.
- The psychological withdrawal symptoms can include psychosis; can be mistaken for a relapse of the disorder
- The withdrawal may also be a trigger for relapse
- Better management of antipsychotic withdrawal may improve outcomes – titrate off slowly as or after new antipsychotic added

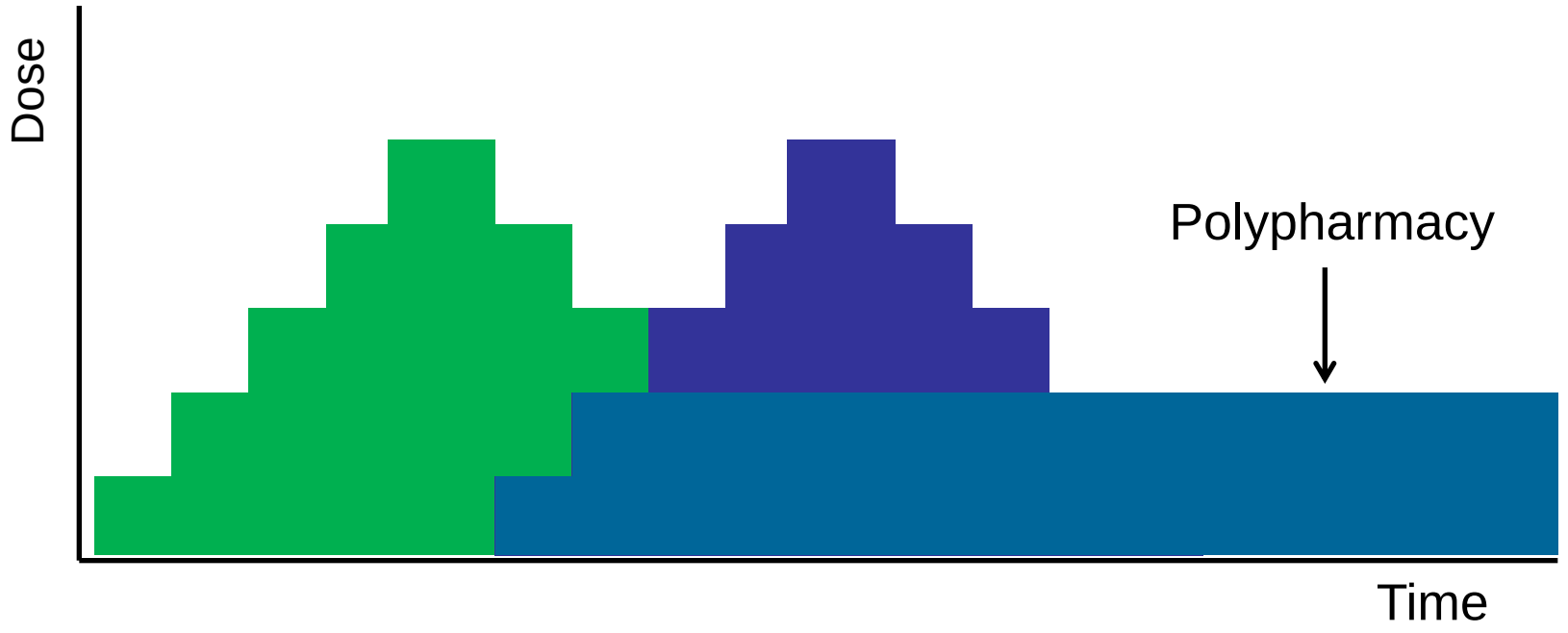
Dilsaver & Alessi. Antipsychotic withdrawal symptoms: Phenomenology and pathophysiology. Acta Psychiatrica Scandinavica 77;3:241–246, March 1988

Cross Titration with Antipsychotics



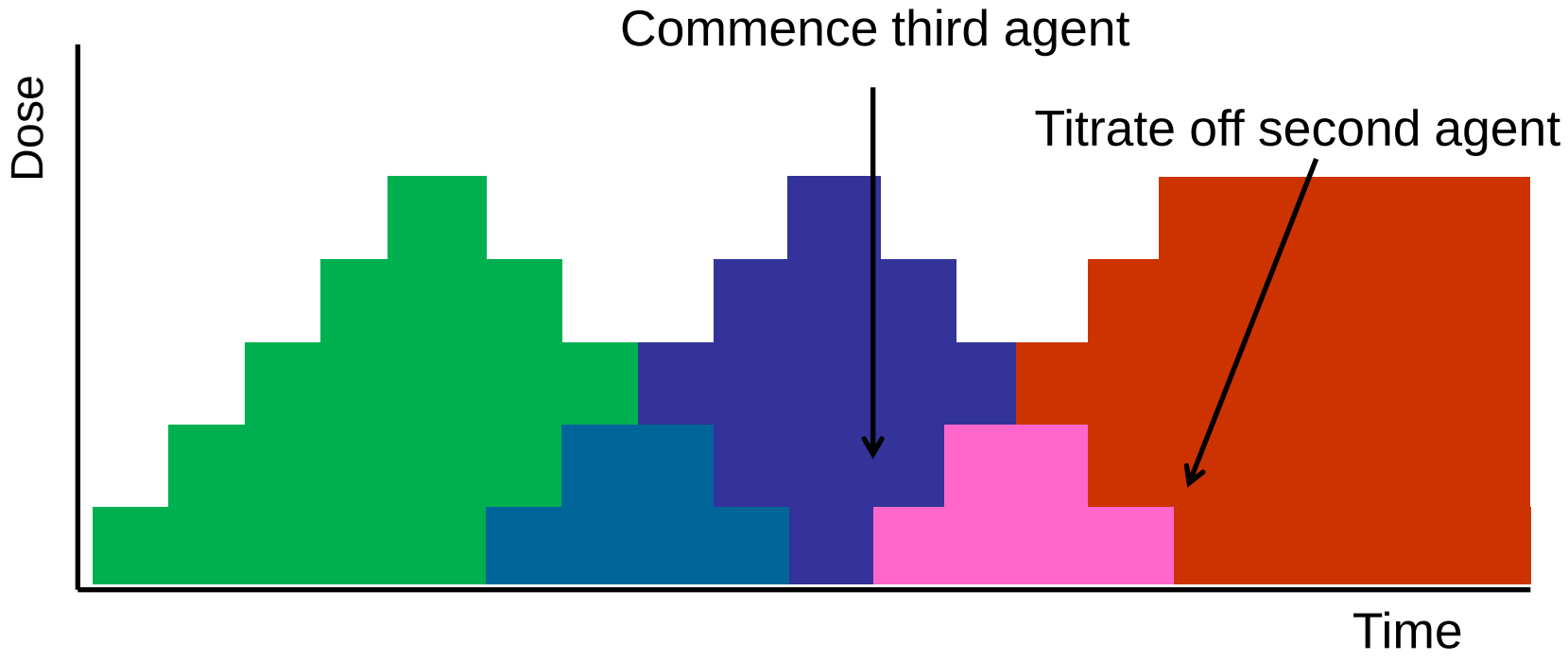
- May not always go to plan depending on response
- Attempt simplest crossover first
- Allow time: the best adjunctive treatment in psychiatry

Cross Titration with Antipsychotics



- It is easy to retain some of the original agent longer than is necessary
- Attempt simplest crossover first
- Allow time: the best adjunctive treatment in psychiatry

Cross Titration with Antipsychotics

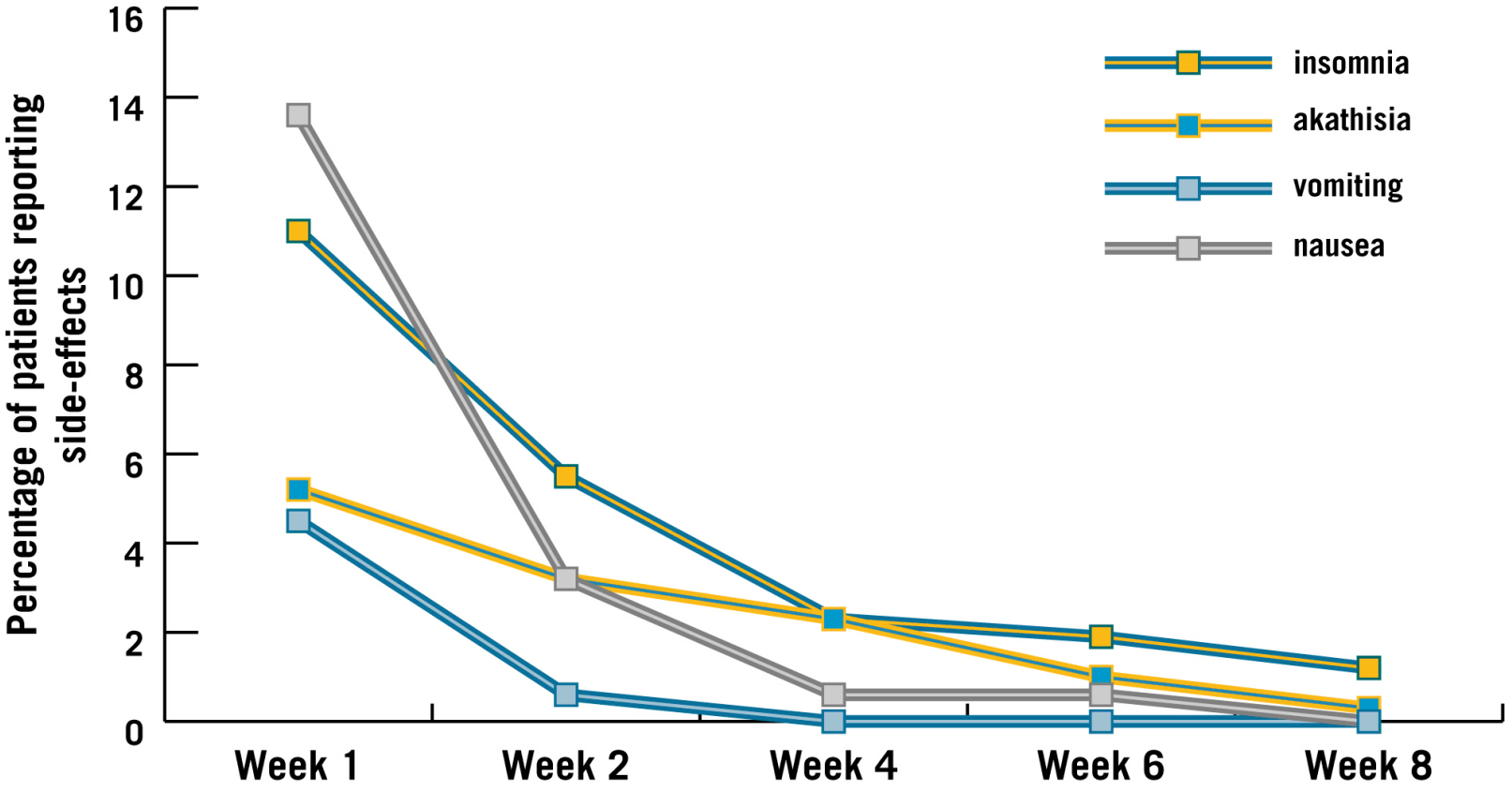


- It may be necessary to trial a third agent
- Allow time: the best adjunctive treatment in psychiatry

Super-Sensitivity Psychosis

- When D_2 receptor antagonists have been occupying the D_2 receptors in the mesolimbic system for a prolonged period of time, up-regulation and super-sensitivity of the D_2 receptors may occur
- When the D_2 receptor antagonist is discontinued abruptly a rapid relapse of psychosis may occur
- When the partial D_2 agonist aripiprazole is introduced a rapid relapse of psychosis may occur
- This relapse has an earlier and quicker onset than what would be expected when an antipsychotic is discontinued.

Aripiprazole: Resolution of Adverse Effects



Data from 8-week switching study

Travis et al., 2005, Int J Clin Pract; 59 (4): 485-95. Casey et al, 2003, Psychopharmacol, 166: 391-399. Casey *et al*., 2002, Poster, Collegium Internationale Neuro-Psychopharmacologicum Congress.

When An Antidepressant Doesn't Work

- Many patients only have a partial response with a few symptoms persisting, especially; insomnia, fatigue and difficulty concentrating
- Some have an initial response and relapse despite continuing antidepressant treatment
- Consider increasing the dose of antidepressant
  - 20mg tablets can be halved for 10mg increments
  - Venlafaxine has a 37.5mg presentation for fine dosing
  - Mirtazapine 30mg tablet can be halved
- Only after treatment with a reasonably effective dose of the first agent for a sufficient period of time and finding either, intolerance or insufficient clinical effect should one consider switching

When An Antidepressant Doesn’t Work

- Ask about current alcohol or other drug use
- Long-term benzodiazepines?
- Not much use throwing an antidepressant their way if the stressors don’t change, may require:
  - Counselling
  - Psychotherapy
  - Occupational therapy
  - Referral for specialist investigation
  - Support groups
  - Self-help on the internet

When Switching Antidepressants be Aware:

- Tricyclic antidepressants carry more risk of switching a bipolar person into a manic episode

- Any antidepressant can cause a switch to hypomania or mania in a person with bipolar disorder uncovering a previously undiagnosed illness

- Tricyclic antidepressants lower seizure threshold more than other antidepressants and are not recommended for people with epilepsy or seizure disorders

Switching Antidepressants: Firstly

- Consider the effect of the addition or removal of enzyme inhibition on concurrent medications:
  - Fluoxetine
  - Paroxetine
  - Sertraline

- Discontinuation effects; especially short half-life agents:
  - Paroxetine
  - Venlafaxine
  - Moclobemide

Switching Antidepressants

- From fluoxetine to MAOI or moclobemide; washout at least five weeks, longer if high dose fluoxetine.
- From fluoxetine to others washout four to seven days.

- From moclobemide to others (inc.MAOI) washout one day
- To an MAOI from any but fluoxetine washout at least seven days
- From TCA to all but MAOI, cautious cross tapering.

- Mirtazapine to SSRI or venlafaxine; cautious cross taper.
- SSRI, TCA, venlafaxine to mirtazapine; cautious cross taper.
- Add an extra week when washout involving clomipramine or sertraline.

Switching Antidepressants

- When switching within a class of antidepressant usually titrate the original antidepressant down to a minimal dose before discontinuing and starting the new antidepressant the next day.

- Cautious cross taper means titrate initial drug down to a half dose or an initial dose,

  e.g.; 10mg fluoxetine, 50mg sertraline, 25-50mg TCA, 37.5mg venlafaxine,

  Then start the next drug similarly. Concurrent for a week, maybe two, then stop the first.

Switching Antidepressants Another View

	Drug switching to			
Initial drug	**Fluoxetine**	**Other SSRI**	**Venlafaxine**	**Mirtazapine**
Fluoxetine		3	1	2
Other SSRI	1	1	1	2
Venlafaxine	1	1		2
Mirtazapine	2	2	2	

1. Direct switch probably safe (or reduce dose to minimal then stop and start)
2. Cross titration recommended
3. Wash-out period recommended

Dr DJ Baxter. http://forum.psychlinks.ca/discontining-or-changing-medications/10999-a-guide-to-switching-antidepressant-therapy.html

Augmentation Therapy

- If the antidepressant is tolerated and has produced some clinical benefit, augmentation could be considered...

- TIME
- Classically,
  - Lithium: requires monitoring and has significant interactions with commonly prescribed medications including; analgesics and antihypertensives
  - Significantly reduces suicide risk
  - Response rate over 50% in two to three weeks!
  - Remains a well evidenced and recommended option.

Augmentation Therapy

- TIME
- Classically,
  - Lithium: requires monitoring and has significant interactions with commonly prescribed medications including; analgesics and antihypertensives
  - Buspirone: may be helpful where there is anxiety
  - Thyroid hormone

- Latterly,
  - Atypical antipsychotics: quetiapine
  - Lamotrigine
  - SSRI or SNRI plus Mirtazapine
  - LOW DOSE Methylphenidate (2.5mg daily, 1-5 days)

Concurrent Antidepressants?!

- Just the same as using multiple antihypertensives, the only pharmacologically rational combinations are with agents that have

  different mechanisms of action.

- SSRI or venlafaxine plus mirtazapine
- SSRI plus bupropion or atomoxetine, but then why not use venlafaxine?

- Trials have shown a single antidepressant produced the same remission rate as two antidepressants and that therapy with two drugs may have more side effects

P. Blier. Am J Psychiatry. 2011;168:689-701

Tricyclic Combinations

- Tricyclic antidepressants have no place in antidepressant polypharmacy, and any potential benefit is outweighed by the increased risk of side effects.

If using tricyclics for pain with concurrent antidepressant either switch to use of the tricyclic for depression also or switch tricyclic to gabapentin for pain

Mirtazapine Plus Antidepressant

- May be synergistic with SSRI or SNRI for severe depression.
- May reverse SSRI or SNRI-induced anxiety and insomnia.
- Mirtazapine may reverse GI effects of SSRI or SNRI.
- Other agents may reverse mirtazapine-induced weight gain.
- Possibly augments haloperidol with efficacy against negative symptoms.

Antidepressant Pearls

- Be alert for cognitive and affective flattening when treating with antidepressants, SSRI and venlafaxine in particular:
  - The person cannot cry like they used to.
- Around 10% of patients suffering a major depressive episode will go on to have a manic episode in the future.
- Consider: psychotherapy, social work, occupational therapy, counselling, social and specific support groups.

Check Compliance

- The most common reason for a lack of effect is not taking the medication as prescribed.

!

Activity of Tricyclic Antidepressants

Antidepressant effect:

Serotonin reuptake inhibition

Noradrenalin reuptake inhibition

Adverse effects:

Alpha adrenergic A1 & A2 antagonism

Histamine H1 & H2 receptor blockade

Acetylcholine (Muscarinic) receptor blockade

Sodium Channel Blockade

Produces quinidine like effect on cardiac conduction:
10-14 days supply may be fatal in overdose

Tricyclic Toxicity

- In the medical literature the lowest reported toxic dose is 6.7 mg per kg body weight.
- Although there are differences in toxicity within the class, ingestions of 10 to 20 mg per kilogram of body weight are a risk for moderate to severe poisoning
- Even doses ranging from 1.5 to 5 mg/kg may present a risk.

Tricyclic Antidepressant Overdose

- Acute overdosage may be accompanied by hypotensive collapse, convulsions and coma
- Absorption is slow but cardiac effects may appear soon after
- Maximal changes in the QRS duration and the T 40ms axis are usually present within 12 hours of ingestion but may take up to a week to resolve
- Sinus tachycardia is the most common arrhythmia due to anticholinergic activity and inhibition of norepinephrine uptake by tricyclic antidepressants but bradyarrhythmias (due to atrioventricular block) and tachyarrhythmias (supraventricular and ventricular) may occur
- Torsade de pointes occurs uncommonly
- Treat acidosis as soon as it appears with intubation if necessary
- Patient should be ventilated before convulsions develop
- Treatment should be continued for at least three days even if the patient appears to have recovered

Case of Mr B

- 36 year old with significant social stressors including charges pending by police
- Previous admission to acute inpatient psychiatric unit with depression and suicidality secondary to similar stressors and charges
- Had been discharged from Community Mental Health Services some months earlier
- Saw GP for poor sleep and somatic complaints
- GP continued amitriptyline 25-50mg nocte for sleep
- Overdosed on 30 day supply of amitriptyline (1500mg)
- BIBA and managed in ICU for three days before transfer to acute inpatient psychiatric unit

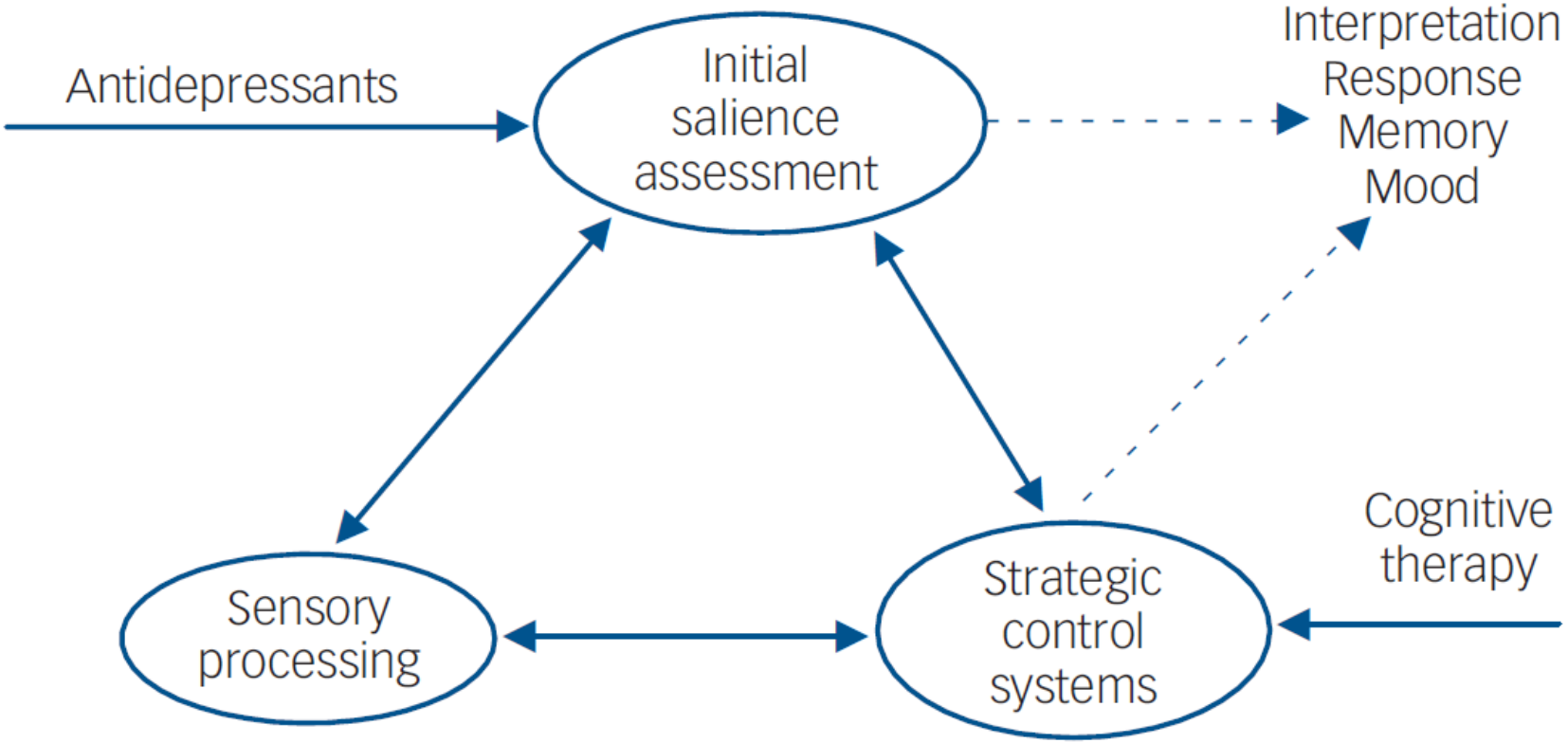
Antidepressant Overdose UK 1994 to 2004

Drugs	All deaths where drug mentioned	Deaths where drug is sole one mentioned	Relative risk: deaths per million prescriptions (sole mention)
Tricyclics	3987	2787	30.1
Of which:			
Dothiepin	2088	1558	48.5
Amitriptyline	1437	932	28
SSRIs	310	71	1
Of which:			
Fluoxetine	115	22	0.8
Paroxetine	67	13	0.6
Citalopram	74	20	1.9

Office of National Statistics United Kingdom

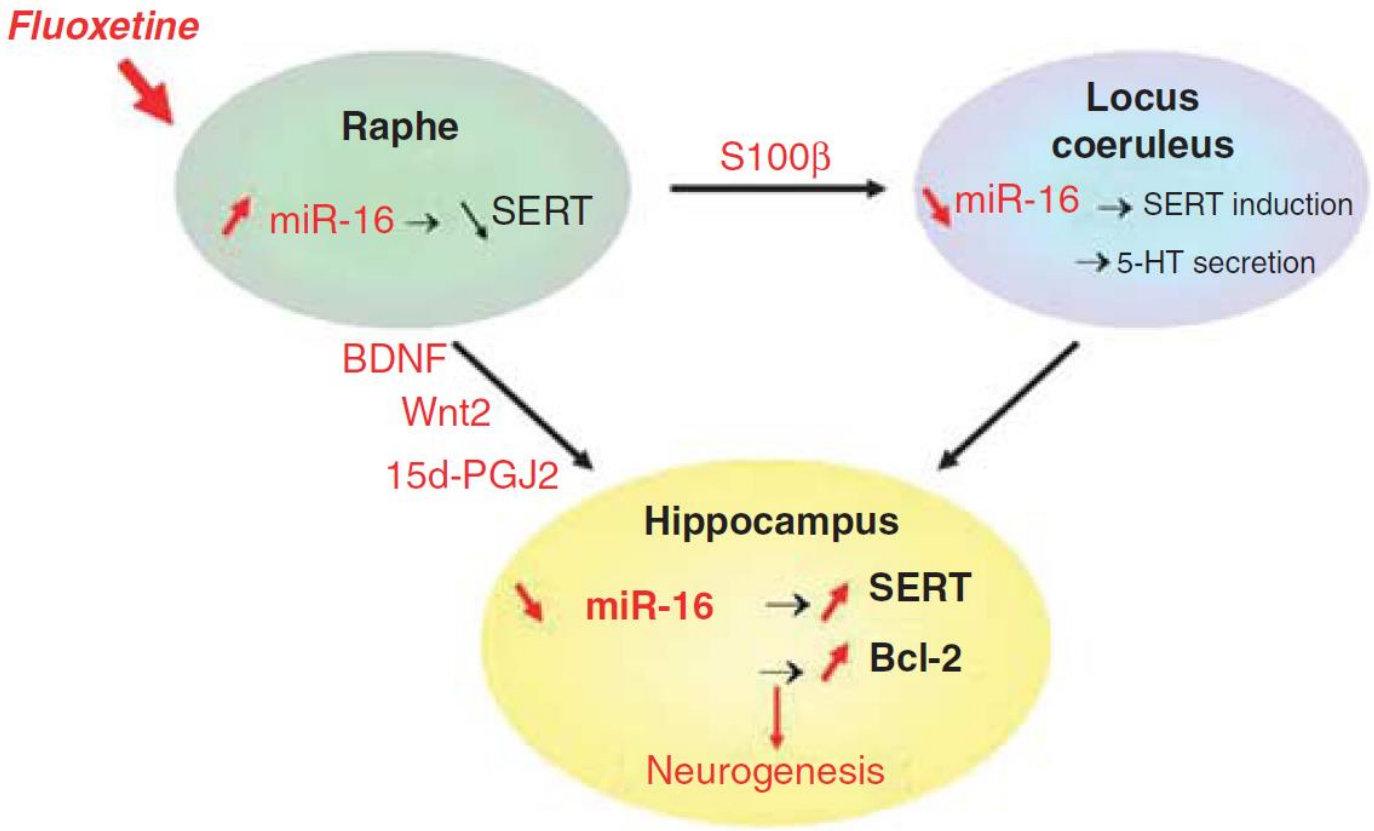
DJ Nutt. Death By Tricyclic: The Real Antidepressant Scandal.
Journal of Psychopharmacology 19(2) (2005) 123–124

Why So Long to Work? Neuropsychology



Harmer, Goodwin, Cowan. The British Journal of Psychiatry (2009) 195, 102–108. doi: 10.1192/bjp.bp.108.051193

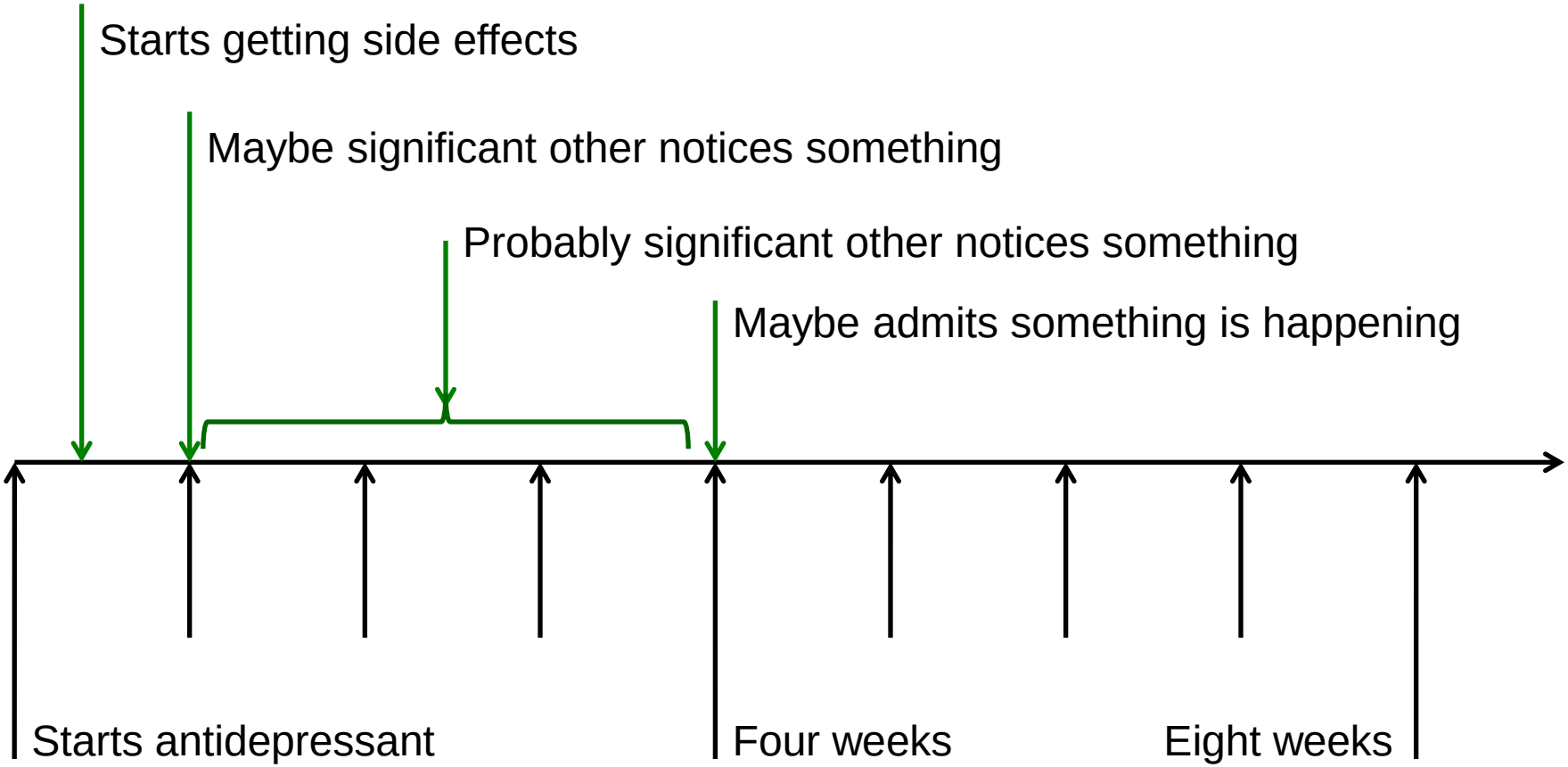
SSRI Neurogenesis? It's Complicated



From a translational research point of view, the therapeutic relevance of the release by the raphe of BDNF, Wnt2 and 15d-PGJ2 is substantiated by our observation that these three factors systematically increase in the CSF of naïve depressed patients after a 12-week fluoxetine treatment.

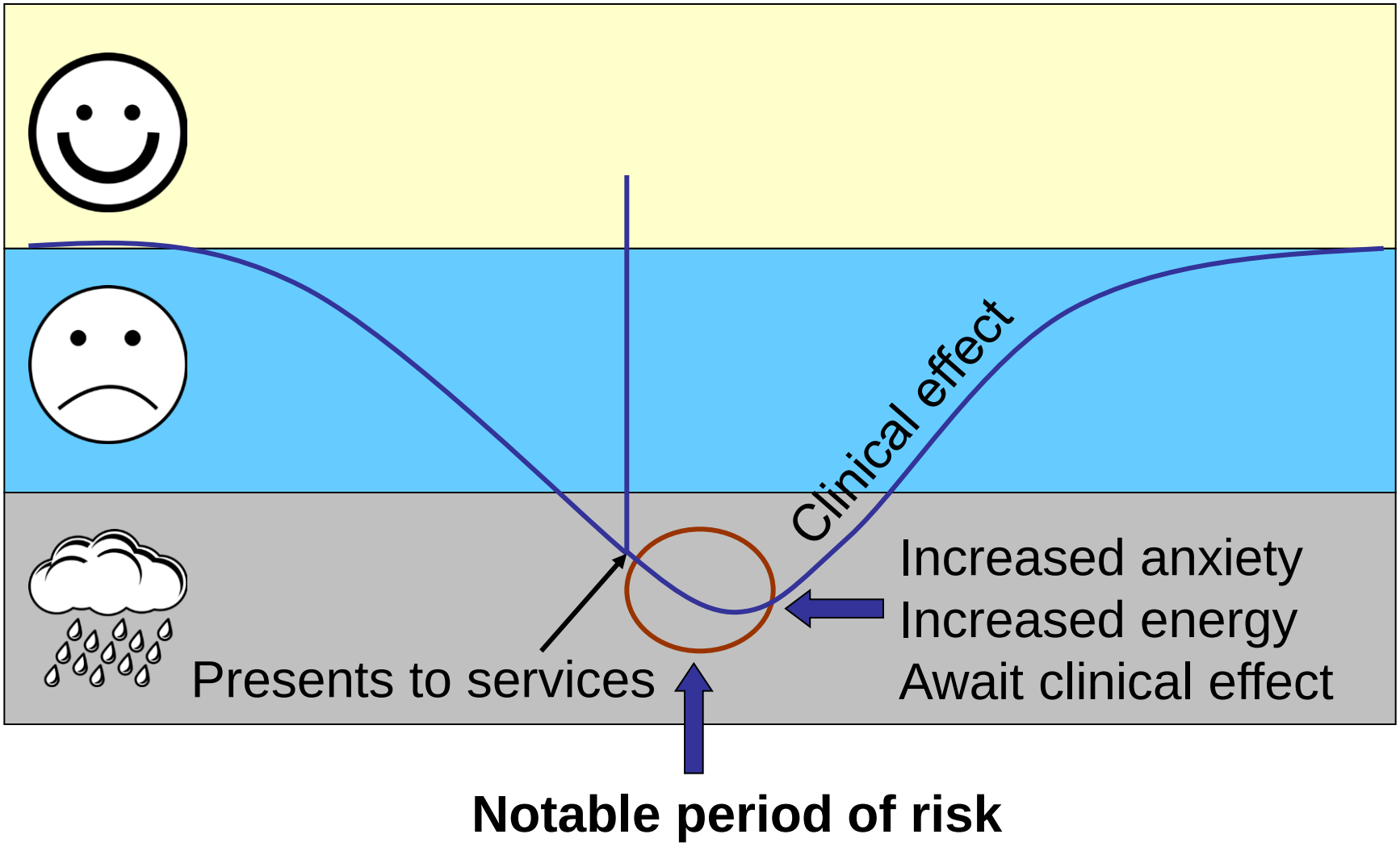
Launay, et al. Translational Psychiatry (2011) 1, e56, doi:10.1038/tp.2011.54

Timeline for Treated Moderate Depression



And then, everyone is different in their response to different antidepressants

Depression Timeline



How Long Must This Go On?

- Some would say a period of one to two weeks is sufficient to see some sort of effect of an antidepressant, but may be subtle:
  - Improvement in mood, behaviour, self-care.
  - Reduced irritability, rumination, guilt.
  - May only be noticed by significant others and not the patient.
- Too unreliable & goes against best evidence guidelines
- A decent trial of an antidepressant should be at least two months, three to six months in the elderly.
- BPAC: Patients should be treated for at least 12 weeks before assessing the efficacy of treatment with a SSRI.

http://www.bpac.org.nz/BPJ/2011/november/antipsychotics.aspx

Commencing an Antidepressant

- Check at two weeks for tolerance.
- If not tolerated:
  - Still compliant?
  - Encourage
  - Reduce dose and start again?
- Wait until fourth week to assess for some clinical benefit
- If unsatisfactory: ask significant other, check for any effect, AOD & compliance, only then increase the dose
- Wait at least four weeks to assess for some clinical benefit
- If unsatisfactory; ask significant other, check for any effect, AOD & compliance, only then increase the dose

Why Drugs Don’t Work

- The patient may not be taking them;
  - If not why not?
  - Intolerance is a big factor: dose too high too fast?
- Dose too low.
- Dose still too low, may have to exceed your expectations.
- Has not been taken long enough to have an effect.
- Check for alcohol, cannabis or other drug use or abuse.
- Non-response to antidepressant therapy in the elderly requires consideration of mild cognitive decline or Alzheimer’s Disease.
- Last consideration; Patient’s illness resistant to this agent.

Antidepressant Deferred

- Miss C, 18 years old
- Inpatient at the Central Region Eating Disorder Service (CREDS)
- For two years GPO and ICAFS had discussed starting an antidepressant but did not do so
- No clear explanation to Miss C of why there was no prescribing
  - Possibly because of age or suicidal ideation
- Doing very much better since antidepressant started

Antidepressants in Adolescents & Youth

- FDA mandated a label warning that antidepressant use can increase suicidal ideation in adolescents and young adults [1].
- Based on 4582 pediatric participants in 24 trials.
- There were no completed suicides in any patients
- But suicidal ideation and suicidal behaviours were nearly twice as common among recipients of antidepressants as placebo [1].
- The FDA decision is likely a factor in the recent decline in antidepressant use among youths [2].
- Interestingly, this decline in antidepressant use appears to have been associated with an increase in suicide rates [3].

[1] Pfeffer CR. The FDA pediatric advisories and changes in diagnosis and treatment of pediatric depression. Am J Psychiatry 2007;164(6):843–6.
[2] Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008;65(1):94–101.
[3] Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007;164(9):1356–63.

Psychotropics, Mental Illness & Pregnancy

- Do NOT change medication immediately
- Best evidence says:
  - Maintain current regimen
  - Minimise if possible
- Seek advice
- If possible; avoid sodium valproate (Epilim) in women of childbearing age
- If possible avoid paroxetine in pregnancy
- For best results: plan the pregnancy

NRAMP

National Register of Antipsychotic Medication in Pregnancy
Prof. Jayashri Kulkarni. Monash Alfred Psychiatry Research Centre
http://www.maprc.org.au/nramp

NICU or SCU admission	14.7%	30.0%
Premature birth	8.3%	9%
Low birth weight <2500g	6.2%	13%
Medication withdrawal signs	?	17%
Neonatal respiratory distress	26.3%	26%
Stillbirths	0.7%	0.8%
Maternal weight gain>15kg	22.4%	33%
Gestational diabetes	5.6%	19.5%
Hypertension of pregnancy	3.8%	2.2%
Antenatal smoking	14%	31%
Antenatal alcohol	51%	19%
Antenatal illicit drugs	8%	11%

Antidepressants During Pregnancy

- Gestational age **may** be shortened by about a week
- **Possibly**; increased risk of bleeding with SSRI, but no effect has been demonstrated on neonatal platelet function tests versus controls
- **Possibly**; increased risk of miscarriage: 12.4% with antidepressants vs. 8.7% in controls
- **Possibly**; insufficient weight gain as a side effect in some women

Bodnar LM et al. (2006), Am J Psychiatry 163(6):986-991; Cohen LS et al. (2000), Biol Psychiatry 48(10):996-1000; Simon GE et al. (2002), Am J Psychiatry 159(12):2055-2061; Hemels ME et al. (2005), Ann Pharmacother 39(5):803-809; Maayan-Metzger A et al. (2006), Acta Haematol 115(3-4):157-161; Rahimi R et al. (in press), Reprod Toxicol; Serebruany (2006)

Neonatal Adverse Effects of Antidepressants

Possibly antidepressant withdrawal effects:

- Respiratory distress, usually mild.
- Tremor, jitteriness.
- Increased REM sleep.
- Fewer different behavioural states.
- Decreased muscle tone.
- Low blood sugar.
- Rare:
  - Seizures.
  - Heart rhythm abnormalities.

Kallen B (2004), Arch Pediatr Adolesc Med 158(4):312-316; Oberlander TF et al. (2004), J Clin Psychiatry 65(2):230-237; Zeskind PS, Stephens LE (2004), Pediatrics 113(2): 368-375

Behavioural Teratogenesis: SSRI & TCA

- Has received minimal attention for medications in general
- Prospective, controlled studies show none [1]:
  - 219 children evaluated age 16 months-7 years
  - 55 children prenatally exposed to fluoxetine
  - 80 children prenatally exposed to TCA
  - 84 controls
  - No differences in: IQ, language development, motor skills, temperament, behaviour

- Fluoxetine protects against brain effects of maternal separation in rats, but it is unknown whether there could be a protective effect in humans

1 Nulman I et al. N Engl J Med 336(4):258-262, 1997

Paroxetine & the FDA

- The FDA have issued a black box warning contraindicating the use of paroxetine during pregnancy due to the risks of cardiac anomalies, FDA 2006

Paroxetine During Pregnancy

- Prospective, controlled studies show no increased risk of anomalies[1]
- Retrospective studies:
  - 1.5x risk of cardiac malformations (1.5%) and
  - 1.8x risk of all malformations vs other antidepressants with 1st trimester exposure
  - 2x risk of cardiac malformations (2%) vs. registry population with 1st trimester exposure
- Most malformations were Ventral Septal Defect (VSD) and ASD

1Schloemp et al. (2006)

Risk of Depressive Relapse in Pregnancy

- N=201 women with history of major depression.
- Prospectively followed over the course of pregnancy.

Relapse status	All No. (%)	Maintained	Increased	Decreased	Stopped
No relapse	115 (57)	61 (74)	11 (55)	22 (64)	21 (32)
Relapse	86 (43)	21 (26)	9 (45)	12 (35)	44 (68)

Cohen LS, et al. JAMA 2006;295:499–507

Risk of Depressive Relapse

- Women who discontinued their medication were at a five-fold greater risk of depressive relapse.
- Pregnancy is **not** protective with respect to risk of relapse of major depression.

Cohen LS, et al. JAMA 2006;295:499–507

Antidepressant Choice During Pregnancy

- Consider better-studied agents:
  - SSRI: citalopram*, escitalopram, sertraline (fluoxetine)
  - Tricyclic with less anticholinergic properties: nortryptiline
- Avoid when possible:
  - Bupropion: preconception, pre-eclampsia
  - Paroxetine: 1st and 3rd trimesters
- Take into account plans to breast feed
- Maybe taper dose over third trimester, consider mother
- Monitor infant for:
  - Poor feeding, low weight gain
  - Irritability
  - Excessive somnolence

1 Wisner KL et al. (1993), Am J Psychiatry 150(10):1541-1542; 2 Hostetter A et al. (2000), Depress Anxiety 11(2):51-57

Dosing Strategies During Pregnancy

- Avoid abrupt discontinuation upon learning of an unexpected pregnancy due to withdrawal effects
- For SSRI and TCA, pharmacokinetic changes may necessitate dose increases as pregnancy progresses[1,2]
- Serum levels can guide dosing of TCA
- Consider partial dose taper during last month of pregnancy to minimize neonatal adverse effects

1 Wisner KL et al. (1993), Am J Psychiatry 150(10):1541-1542

2 Hostetter A et al. (2000), Depress Anxiety 11(2):51-57

Antidepressant Choice During Breastfeeding

- Consider better-studied agents:
  - SSRIs: citalopram, escitalopram, paroxetine, sertraline.
  - Tricyclics with low anticholinergic and lower sedative properties: desipramine, nortryptiline.
- Monitor infant for;
  - Poor feeding, low weight gain
  - Irritability
  - Excessive somnolence

Considerations - Planning

- Planned pregnancy
- Team approach
- Folate 0.8 mg/day, more if taking anticonvulsants.
- Optimization of medication therapy
  - Monotherapy
  - Lowest effective dose
  - Modified release formulations
  - Non-depot typical antipsychotics
  - Prior to conception

Case of Mrs D

- 28 year old woman, 30/40 pregnancy
- Psychotic and suicidal, husband found her in garage preparing a rope with intent to hang
- Depressed previous twelve months and had been on fluoxetine until pregnancy recognised
- GP checked with a psychiatrist who may have recommended change to sertraline, was switched
- Concurrent stressors:
  - Relationship issues
  - Moved from one city to another to live with mother
  - Loss of employment and change in financial situation
  - Pregnant

Adverse Effects & Interactions of Interest

A Case of What's Going On?

- 29 yr old male presents to ER intoxicated, wife present
- Wife states that he hasn't been himself for the past few months, was diagnosed with depression and started on a SSRI three months ago. Responded well
- Recently feeling so good and energetic that he found he needed less sleep he is now sleeping 2-3 hrs a day
- Has been showering his wife with expensive gifts and has hit the maximum limit on all of their credit cards
- Has been extremely romantic and more interested in sexual relations than at any time before
- Has also started drinking heavily and his boss said that he is in danger of being fired if things don't straighten out
- Intoxication aside, physical exam & blood tests normal

Common Drugs That May Induce Psychosis

Sympathomimetics

- Amphetamines, methylphenidate

Antiinflammatory drugs

- Steroids – prednisone doses >20mg daily

Anticholinergic drugs

- Benztropine, procyclidine

Hallucinogens

- LSD

Dopaminergic agents, especially in schizophrenics

- L-Dopa

Common Drugs That May Cause Anxiety

Stimulants

- Amphetamine, aminophylline, caffeine, cocaine, methylphenidate, theophylline, party pills

Sympathomimetics

- Adrenaline, ephedrine, phenylpropanolamine, pseudoephedrine

Anticholinergics

- Benztropine, diphenhydramine, oxybutinin, TCA withdrawal

Dopaminergics

- Amantadine, bromocriptine, levodopa, metoclopramide, neuroleptics

Miscellaneous

- Baclofen, hallucinogens, indomethacin, pethidine, cannabis, nicotine

Drug withdrawal

- Alcohol, barbiturates, benzodiazepines, narcotics, sedatives

Akathisia May Look Like Anxiety

- Uncontrolled sense of inner restlessness
- If mistaken for anxiety and the antipsychotic dose is increased may worsen the restlessness
- May not be intolerable or particularly disfiguring
  - So may not require intervention
- Can be managed with antipsychotic dose adjustment
- Can be managed with a small dose of propranolol - initially 10mg BD with small steps up to 40mg BD
  - Caution re side effects, interactions and nightmares

Interactions

- Paroxetine increases procyclidine plasma levels
- Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme.
- TCA: amitriptyline, nortriptyline, imipramine, desipramine
- Antipsychotics: Thioridazine, risperidone
- Certain Type 1c antiarrhythmics: propafenone, flecainide
- Metoprolol, atomoxetine
- Tamoxifen: endoxifen is an important active metabolite, irreversible inhibition of CYP2D6 by fluoxetine or paroxetine lowers plasma concentrations of endoxifen

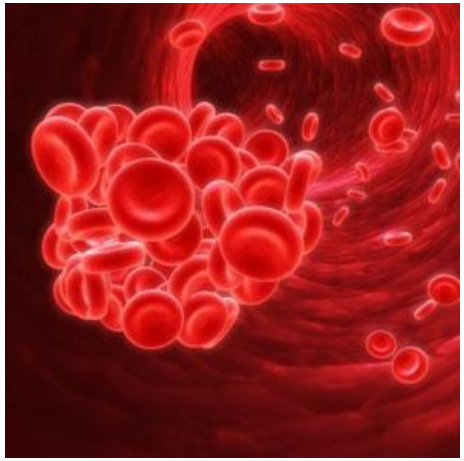
- **Avoid either during treatment with tamoxifen**

http://www.bpac.org.nz/magazine/2007/march/interactions.asp

Antidepressants and Warfarin

- Warfarin users who initiated citalopram, fluoxetine, paroxetine, amitriptyline, or mirtazapine had an increased risk of hospitalization for gastrointestinal bleeding:

  - Amitriptyline OR 1.47 (1.02-2.11)
  - Citalopram OR 1.73 (1.25-2.38)
  - Fluoxetine OR 1.63 (1.11-2.38)
  - Mirtazapine OR 1.75 (1.30-2.35)
  - Paroxetine OR 1.47 (1.02-2.11)



- Monitor INR and have patient report signs of bleeding

Schelleman. PLoS ONE June 2011 6;6:e21447

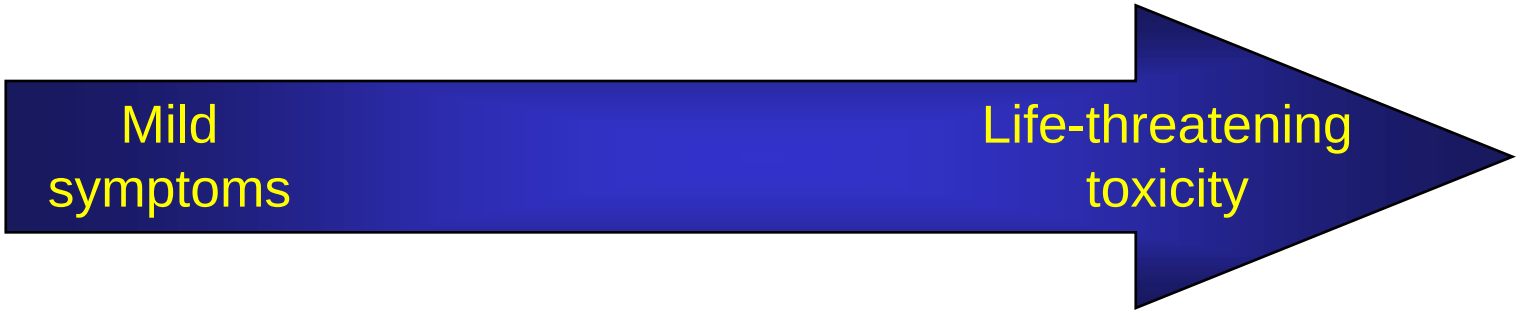
http://www.bpac.org.nz/magazine/2007/april/warfarin.asp

Serotonin Toxicity (Serotonin Syndrome)

- Predictable consequence of excessive serotonergic agonism in the central and peripheral nervous system
- Excess serotonin produces a spectrum of clinical findings:
  - change in mental status e.g.: confusion
  - agitation
  - myoclonus
  - hyperreflexia
  - sweating
  - tremor
  - diarrhoea
  - incoordination
  - fever

Clinical Manifestations of SS

Akathisia	Hypertension	Clonus (sustained)
Diaphoresis	Hyperthermia <40^{O}C	Hyperthermia >41^{O}C
Mydriasis	Tachycardia	Hypertension



Shivering	Altered mental status	Muscular hypertonicity
Tremor	Clonus (inducible)	Tachycardia
	Hyperreflexia	⇨ Shock

Boyer EW, Shannon M. The Serotonin Syndrome
New England Journal of Medicine 2005;352:11 12-20

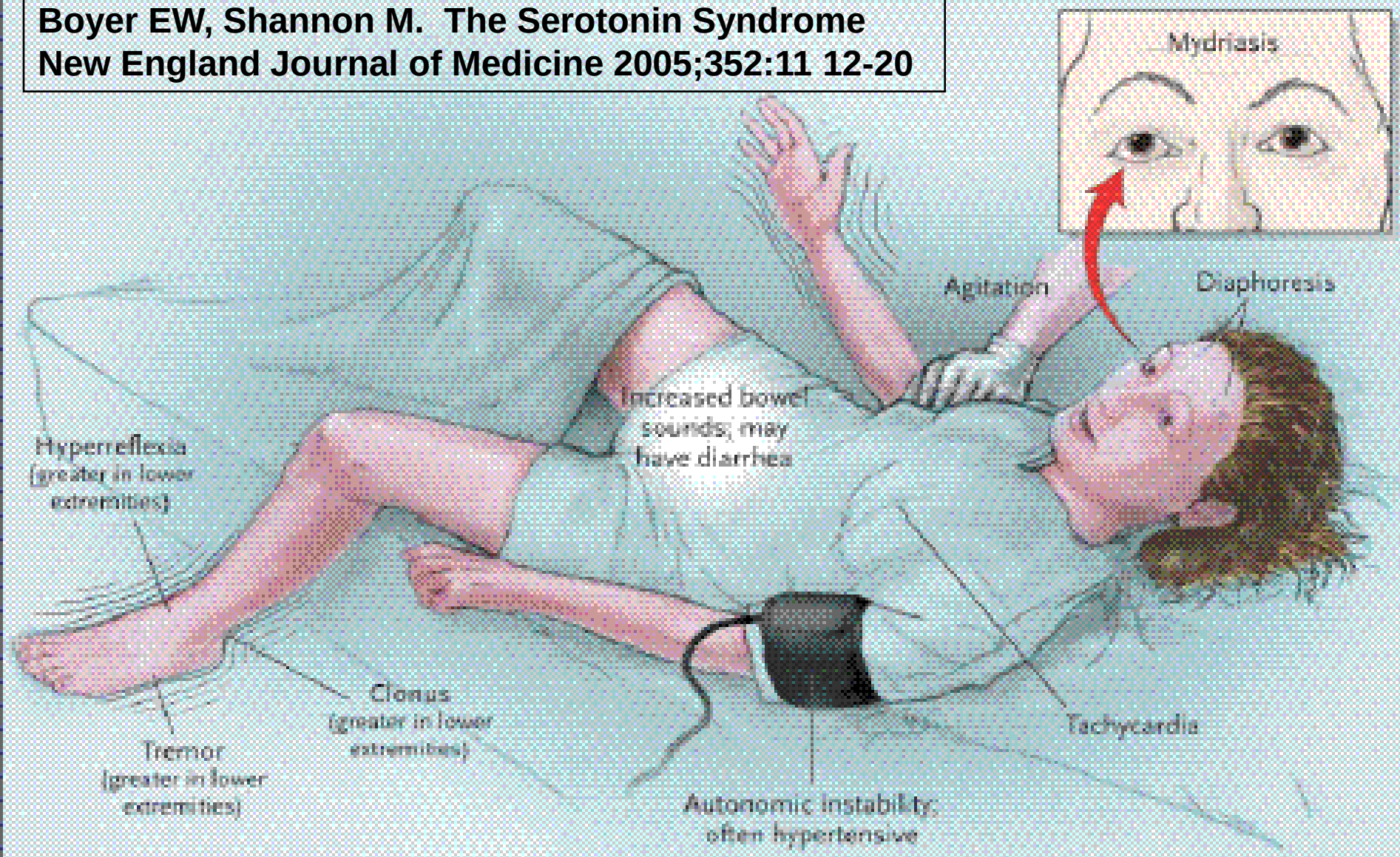
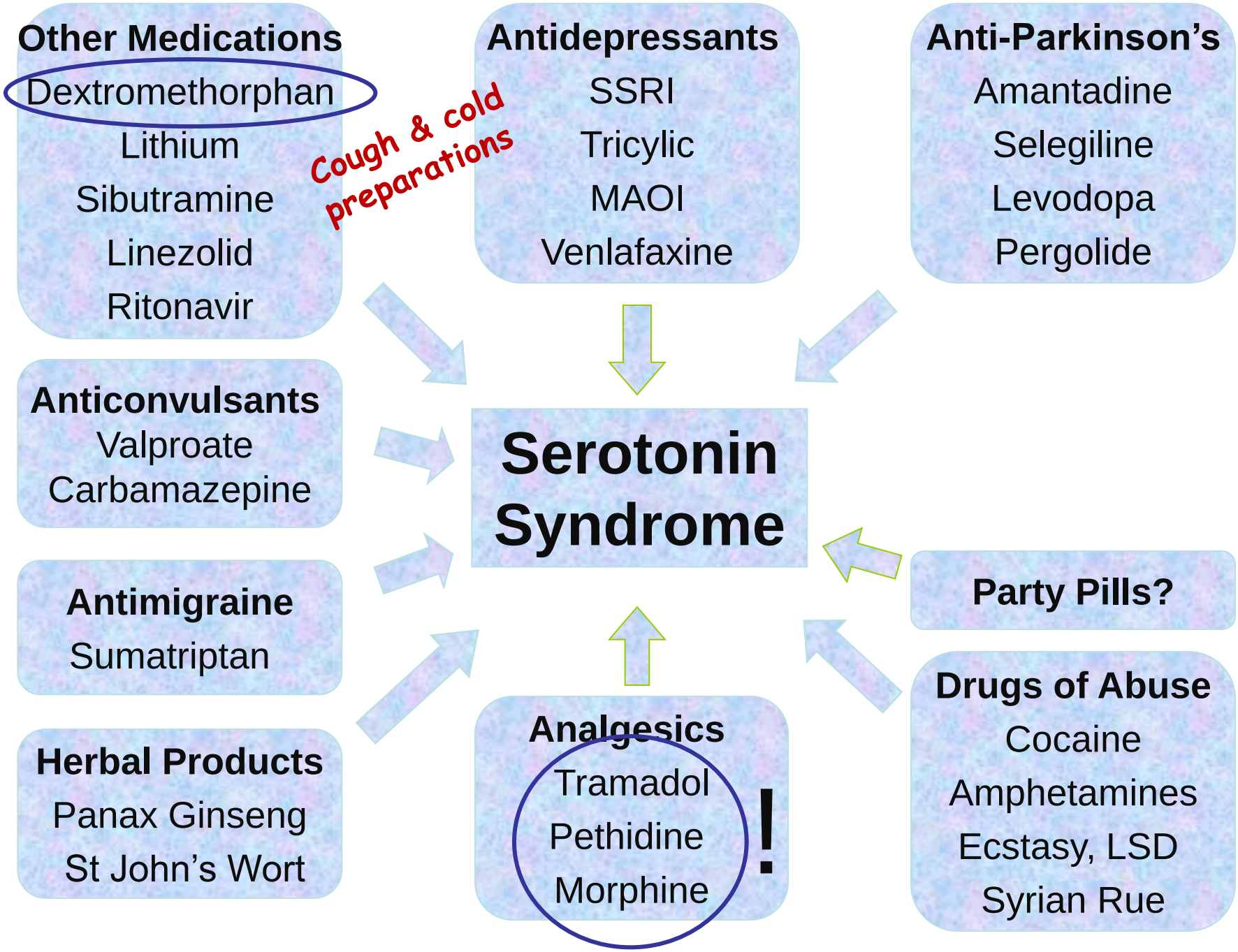


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

Serotonin Toxicity Drugs of Concern

- Antidepressants
  - SSRI
  - TCA
  - MAOI*
  - Moclobemide
- Saint John’s Wort
- Tramadol


Other Medications
Dextromethorphan
Lithium
Sibutramine
Linezolid
Ritonavir
Cough & cold preparations
Antidepressants
SSRI
Tricylic
MAOI
Venlafaxine
Anti-Parkinson's
Amantadine
Selegiline
Levodopa
Pergolide
Anticonvulsants
Valproate
Carbamazepine
Serotonin Syndrome
Antimigraine
Sumatriptan
Party Pills?
Herbal Products
Panax Ginseng
St John's Wort
Analgesics
Tramadol
Pethidine
Morphine
!
Drugs of Abuse
Cocaine
Amphetamines
Ecstasy, LSD
Syrian Rue

Varenicline: Champix

- Varenicline is a partial agonist of the α4β2 subtype of the nicotinic acetylcholine receptor.
  - In addition it acts on α3β4 and weakly on α3β2 and α6-containing receptors.
  - Varenicline is an agonist at α7-receptors
  - Varenicline is an agonist at 5-HT3 receptors
- Thought to aid in smoking cessation by activating nAChR enough to prevent withdrawal while limiting the rewarding effect of nicotine

Dysregulation of the cholinergic system might contribute to the etiology of major depressive disorder, but it is complicated and poorly understood. Mineur & Picciotto. Trends Pharmacol Sci. 2010 December; 31(12): 580–586. doi:10.1016/j.tips.2010.09.004

Some Risk Due to 5-HT3 Agonism

5-HT3 agonists increase:

- Nausea and vomiting by N&V centre in brain stem
- Anxiety through activity in the amygdala
- Depression through activity in the hippocampus
- Lower seizure threshold

- Yet; Gunnell et al, found no clear evidence of an increased risk of self harm, suicidal thoughts, or depression in people prescribed varenicline compared with those prescribed other smoking cessation products.
- Although a halving or a twofold increased risk of self harm with varenicline cannot be ruled out

Gunnell et al. Varenicline and Suicidal Behaviour. BMJ 2009;339:b3805 doi:10.1136/bmj.b3805

So What?

- Psychiatric symptoms have been described secondary to initiation of varenicline including:
  - Depression, aggression, agitation, insomnia, anger, abnormal dreams, insomnia, hallucination
  - There have also been reports of self-injurious and suicidal ideation or behaviour.
- While some people have experienced these types of symptoms as a result of nicotine withdrawal, it appears increasingly likely with accumulating experience that there is an association between varenicline and serious neuropsychiatric events in some people

- <u>Be sure the patient knows what to expect and monitor</u>

Case of Mr C

- Mr B, 36 years old, no psychiatric history
- Went to GP wanting help to give up cannabis
- GP prescribed Champix with added citalopram in case he gets a little anxious
- Hypomanic episode
  - Reduced sleep and appetite
  - Increased irritability and anxiety, persecuted
  - Disorganised thinking and behaviour
  - Increased impulsivity
- BIBP to acute inpatient psychiatric unit, charges pending
- Resolved in days and discharged
- Cannabis remained a problem

Causes of Hyponatraemia

- Hypotonic Hyponatraemia
  - Reduced Water Excretion
    - Increased Extracellular fluid volume
    - Normal Extracellular fluid volume
    - Decreased Extracellular fluid volume
  - Excess Water Intake
- Isotonic Hyponatraemia
- Hypertonic Hyponatraemia

<u>Renal Failure eg;</u>
Diuretic +
ACEI or A2RA +
COX2A or NSAID

Diuretics
SIADH:
Ca Chemotherapy
Antipsychotics
Antidepressants
Bromocriptine
Amiodarone
Ciprofloxacin
Ecstasy

<u>Polydipsia;</u>
Lithium
Party Pills?

Drugs Commonly Associated with Hyponatraemia

- Diuretics (all)
- Antidepressants: SSRI, SNRI > Others > MAOI
- Carbamazepine
- ACE Inhibitors
- COX-2 Inhibitors & NSAID
- Hypnotic agents
- Antipsychotics
- Chemotherapy
- Sulphonylureas: glipizide, glibenclamide, gliclazide potentiate ADH
- Hormone analogues: DDAVP (ADH), oxytocin
- Proton Pump Inhibitors: omeprazole, pantoprazole
- Recreational drugs: ecstasy, party pills?

Clinical Presentation Varies

- Most commonly described disorders:
  - Neurological: convulsions, altered consciousness or coma, somnolence, headache, visual disturbances, cerebral oedema
  - Postural hypotension, syncope
  - Psychiatric: confusion, delirium, agitation, hallucinations
  - Gastrointestinal: anorexia, nausea, vomiting
- Of most concern:
  - Acute Illness, Neurological Symptoms, Dehydration Comorbid Chronic Disease, Failure to Respond to Treatment, Severe Hyponatraemia (Na^+ <120mmol/l)

Phone a Friend: Mental Health Service

- Psychogeriatrics; Clinical Nurse Manager
  MH Pharmacist
- Acute Inpatient Unit; Clinical Nurse Manager
  MH Pharmacist
- Community Mental Health; Team Leader
  MH Pharmacist
- Crisis (CATT) Team, Eating Disorders Service, Child & Family Services, Maternal Mental Health

Useful References

- BPAC on Polypharmacy: http://www.bpac.org.nz/resources/campaign/polypharmacy/bpac_polypharmacy_poem_2006_pf.pdf
- www.epilepsyandpregnancy.co.uk
- www.patient.co.uk