

DEPRESSION: A FORGOTTEN EPIDEMIC

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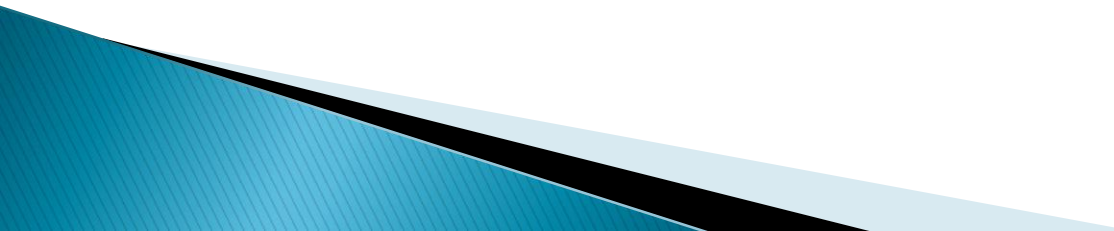
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Epidemiology

- ▶ The Global Burden of Disease Study from the WHO identifies MDD as the 4th leading cause of the global disease burden & the leading cause of disability worldwide
- ▶ The results of the South African Stress and Health Study (SASH survey) was recently published & is the first large scale epidemiological study of the prevalence rates of MDD in Africa—was carried out in conjunction with the WHO World Mental Health Survey Initiative. It was found that the prevalence for major depression in RSA was 9.7% for lifetime & 4.9% for 12 months:
 - prevalence was >among females
 - > in those with a low level of education (below grade 8)
 - >in people between 40–49yrs
 - >90% of all the respondents with depression reported global role impairment. RSA has lower rates of depression than the USA but higher rates than Nigeria. The findings indicate that MDD is a seriously impairing condition in RSA & the level of mental health services in the country needs to improve

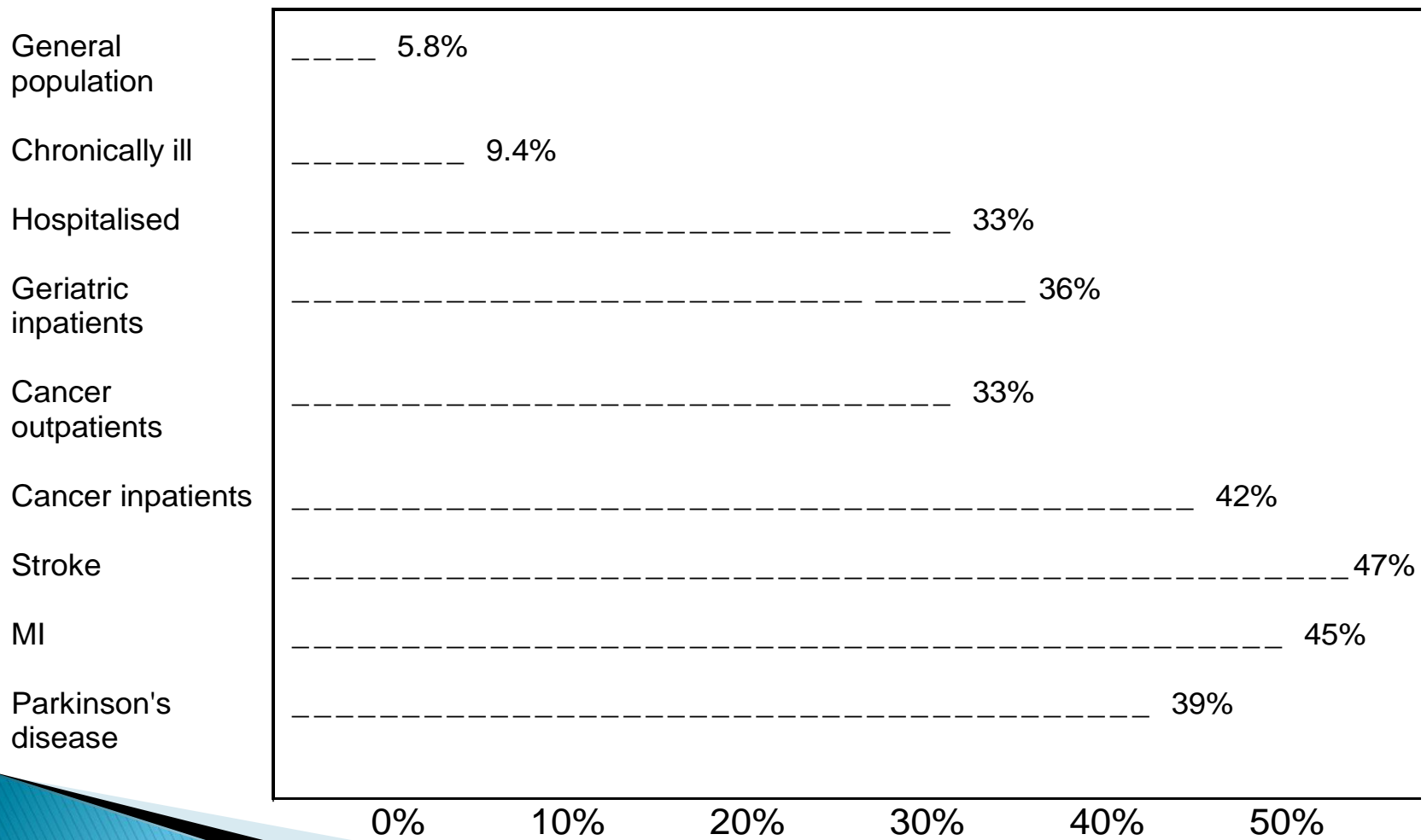
Depression

Epidemiology of clinical depression

- Depression is a common illness affecting 11,5 million people - about 1 in 20 - every year.
 - Depression occurs twice as often in women as it does in men.
 - Depression is seen in all age, racial, socio-economic, and ethnic groups.
 - 6-8% of primary care patients have major depression.
 - Diagnosis of depression is missed in primary care in up to 50% of cases.
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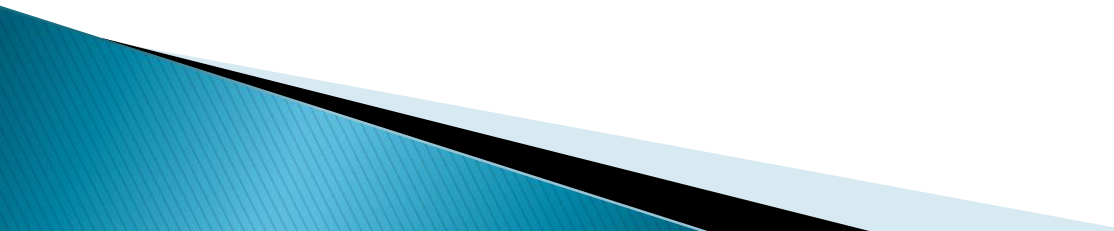
Etiology and pathogenesis of depressive disorders

- Neurobiologic factors
- Psychosocial factors
- Developmental factors



**There is a range of percentages depending on the study.*

The syndrome of depression

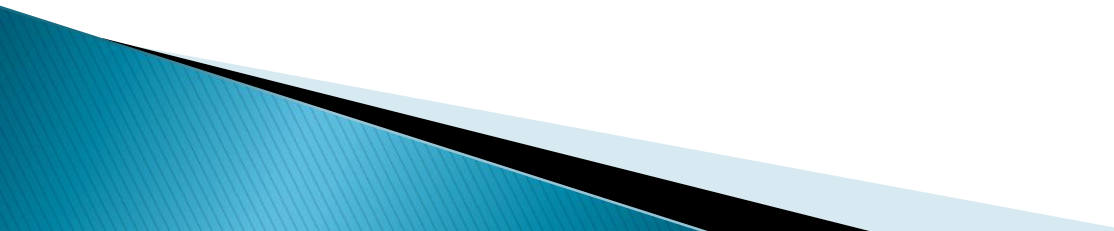
- A constellation of signs and symptoms which vary from patient to patient.
 - An expression of multiple factors often superimposed upon an intrinsic vulnerability (genetic/developmental).
 - May represent a primary psychiatric disorder or be a secondary feature of other disease processes, drug effects, or environmental stressors.
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Diagnostic features of major depression

- **General criteria**

- Depressive episode lasting at least 2 weeks.
- Not attributable to other organic factors.
- Absence of hypomania or mania.

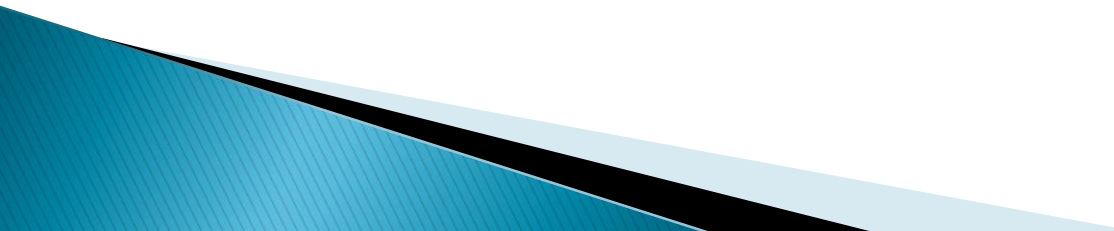
▶ **Typical symptoms**

- Depressed mood present most of the day and almost every day.
 - Loss of interest or pleasure in usual activities.
 - Decreased energy or increased fatigability.
 - Loss of confidence or self-esteem.
 - Unreasonable feelings of guilt.
 - Recurrent thoughts of death or suicide.
 - Complaints of diminished ability to think or concentrate.
 - Change in psychomotor, with agitation or retardation.
 - Sleep disturbances.
 - Change in appetite.
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Why the Concern?

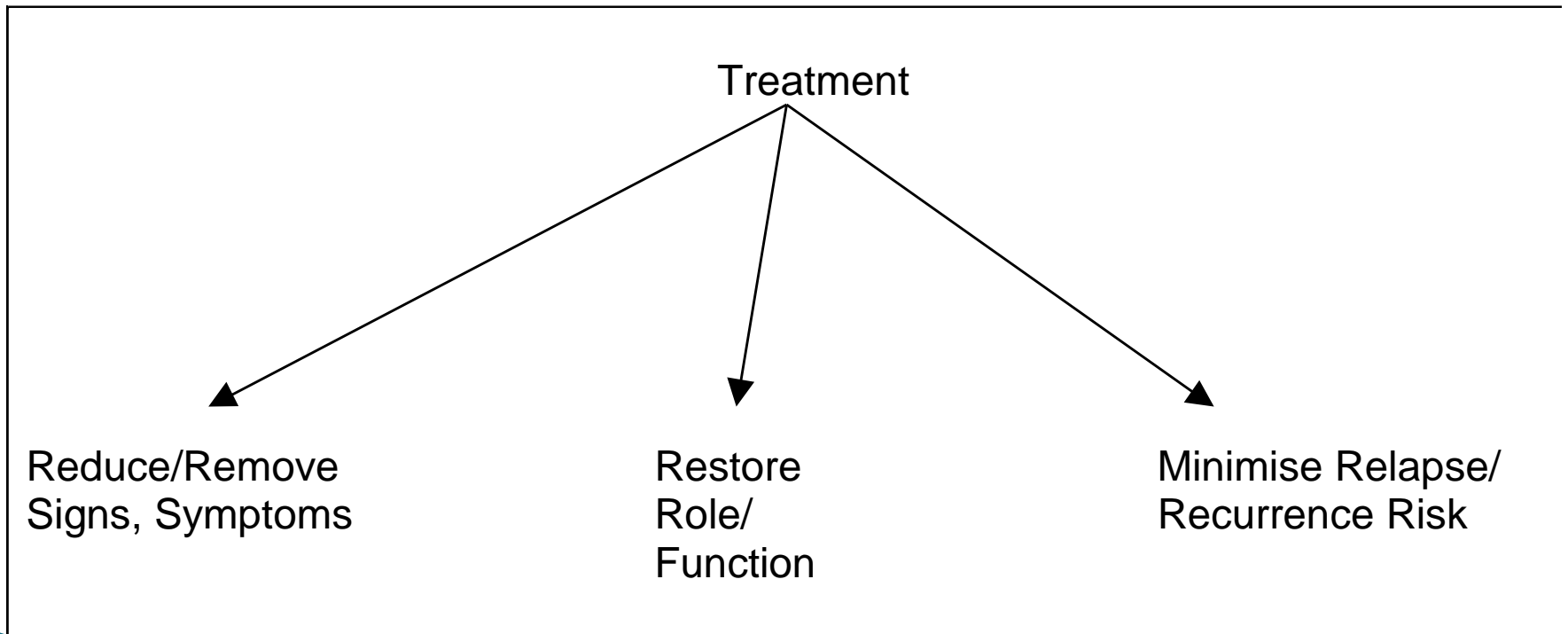
- **Long-term implications of clinical depression**
 - Increase in morbidity and mortality
 - Prolonged disability
 - Impaired functioning
 - Economic burden to society

Suicide rates due to depressive disorders

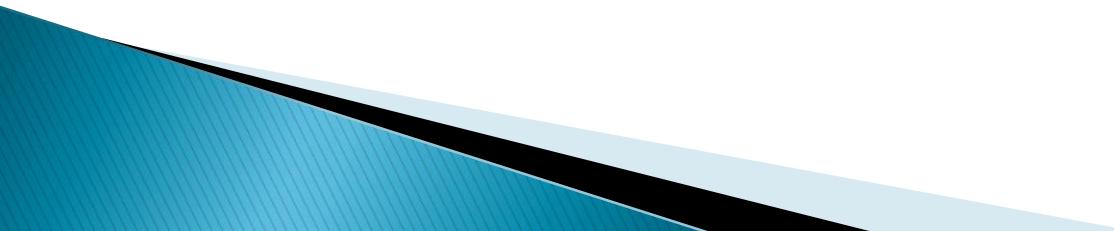
- Two-thirds of depressed patients exhibit suicidal ideation.
 - 10%-15% of depressed patients commit suicide.
 - Despite the clinical, social, and economic burdens, depression is underrecognized and inadequately treated.
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Treatment

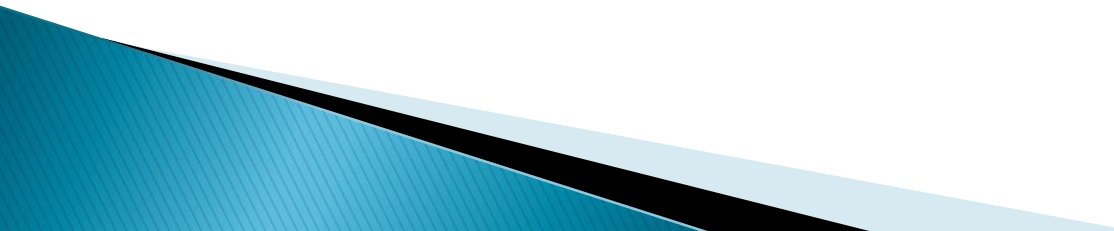
Treatment Goals



Principal treatment options for major depression

- Antidepressant medications
 - Psychotherapy
 - ECT
 - Combination of the above
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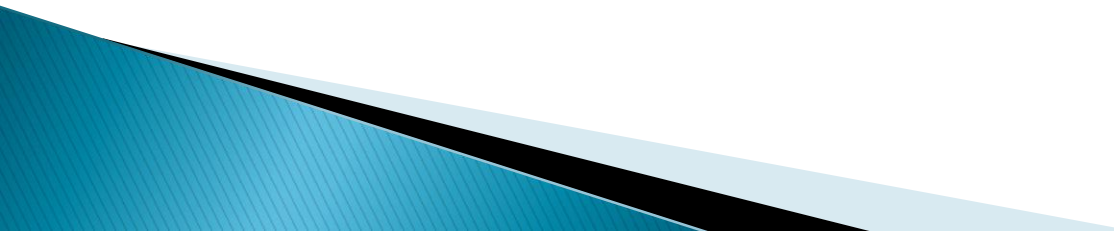
Clinical management: obstacles to compliance

- Disease characteristics (e.g. helplessness, pessimism).
 - Delayed symptomatic response.
 - Stigma and discrimination attached to diagnosis and treatment.
 - Drug side effects.
 - Noncompliance.
 - Patient's personality.
- 

Indications for maintenance treatment

- ≥ 3 episodes of a depressive disorder.
- 2 episodes and previous recurrence within 1 year; severe, sudden, life-threatening episodes in past 3 years.

Indications for antidepressants

- ▶ symptom severity.
 - ▶ hypothalamic dysfunction.
 - ▶ potential disease-associated complications.
- 

Classes of antidepressant medications

| TCAs, e.g. | SSRIs, e.g. |
|---|--|
| Amitriptyline Clomipramine Imipramine | Fluvoxamine Citalopram Fluoxetine Paroxetine Sertraline |
| SNRI | Other agents, e.g |
| Venlafaxine | Amineptine Amoxapine Bupropion Mianserin Mirtazapine Nefazodone Tianeptine |
| MAO's, e.g. | RIMA |
| Isocarboxazid Phenelzine | Moclobemide |

Possible clinical side effects of blocking various receptors

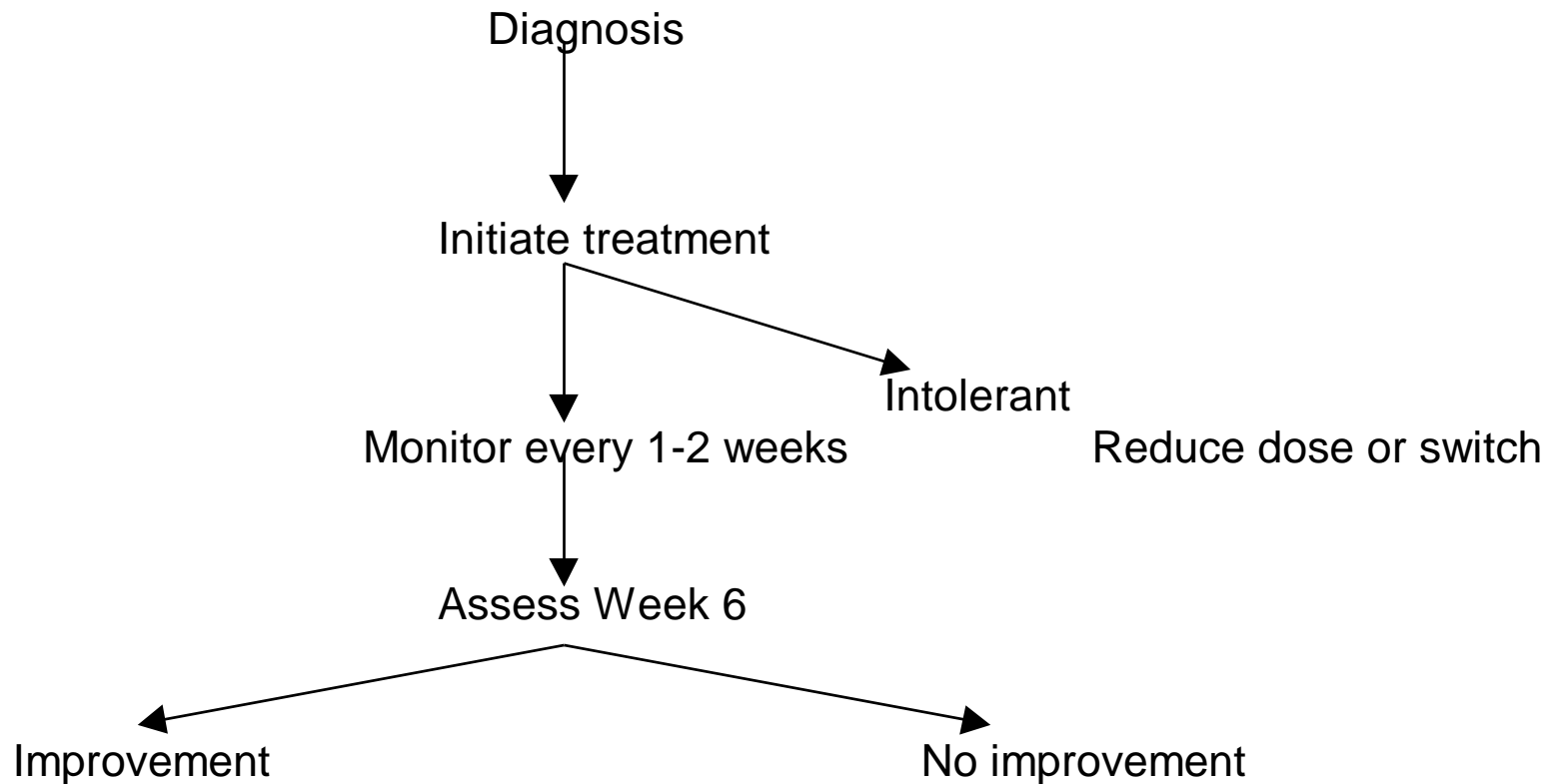
| Blockade of: | Possible clinical consequences: |
|----------------------------------|---|
| Muscarinic receptors | Blurred vision; dry mouth; sinus tachycardia; constipation; urinary retention; cognitive dysfunction |
| α_1 -adrenergic receptors | Potential of the antihypertensive effect of prazosin and terazosin; postural hypotension; dizziness; drowsiness; reflex tachycardia |
| α_2 -adrenergic receptors | Blockade of the antihypertensive effects of clonidine and α -methyldopa |
| Dopamine D_2 receptors | Extra pyramidal movement disorders |
| Histamine (H_1) | Sedation; weight gain |
| Na^+ - K^+ channel | Cardiovascular, e.g. arrhythmia |

Side-effect profiles

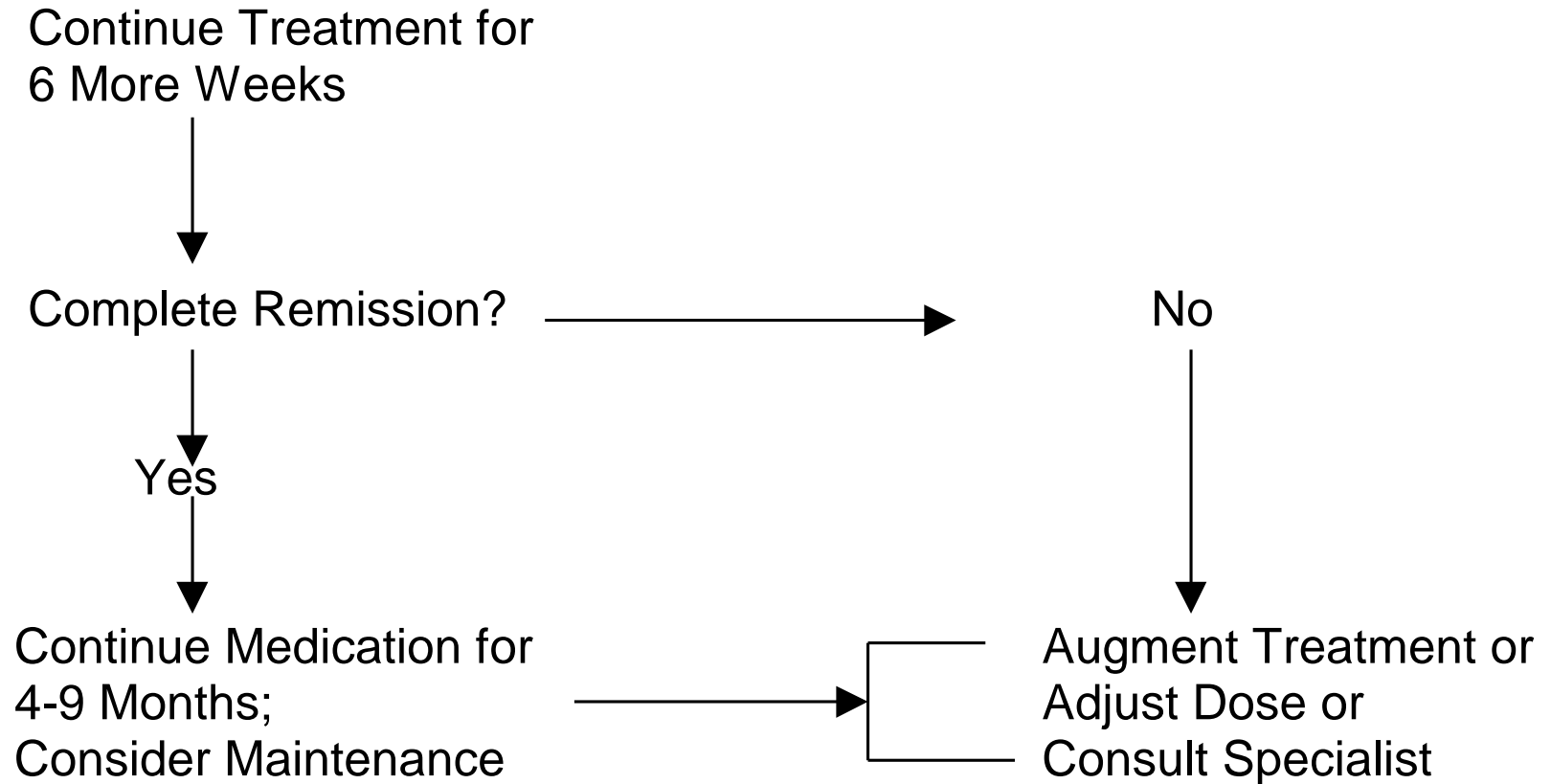
| Tri Cyclic Antidepressants (TCAs) | SSRIs |
|--|---|
| Dry mouth Blurred vision Constipation Sedation, drowsiness Weight gain Postural hypotension Cardiac effects Dizziness | Nausea Nervousness Insomnia Sexual dysfunction Headache |

Treatment with antidepressant

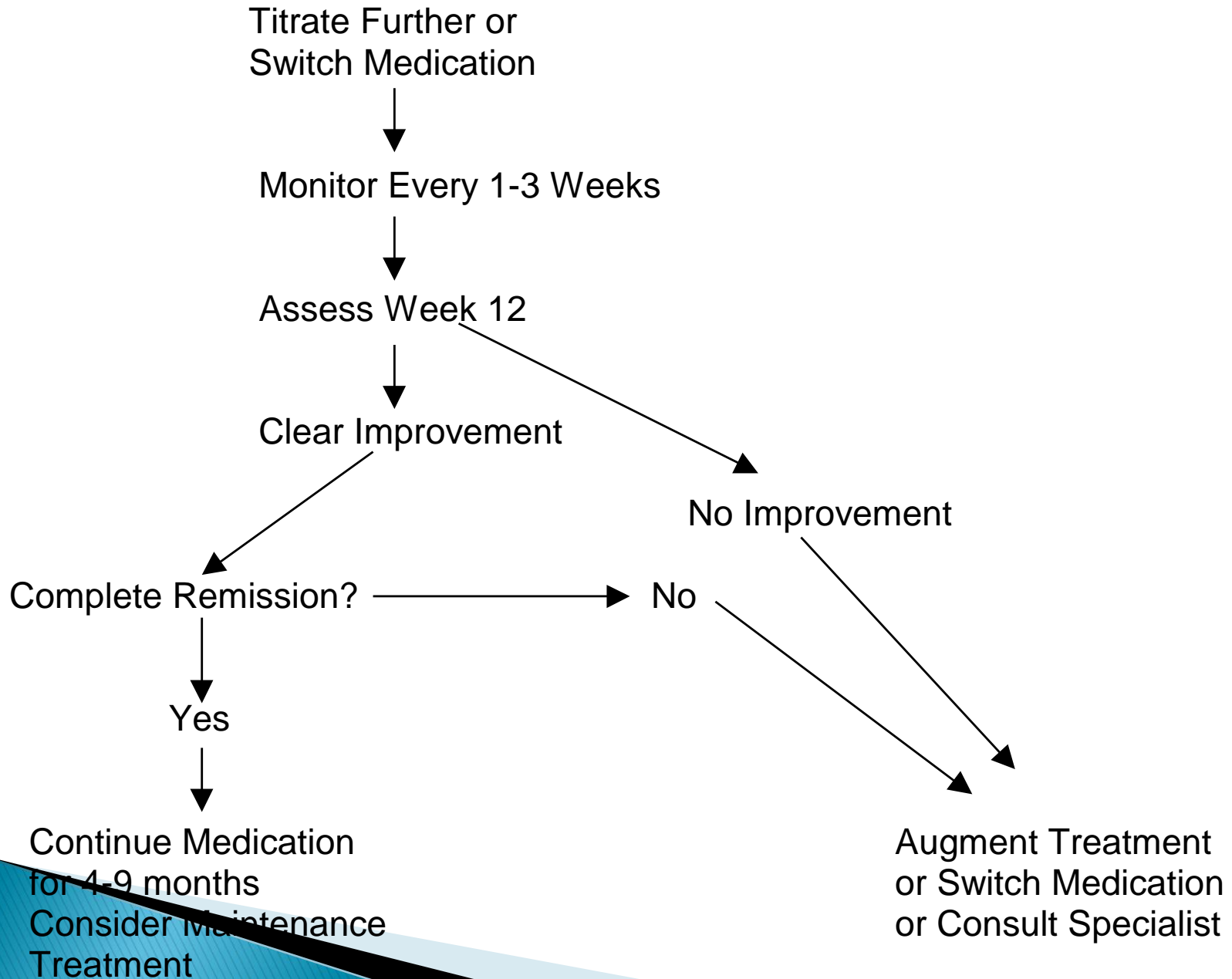
Acute phase



Six-week assessment: clear improvement



Six-week assessment: no improvement

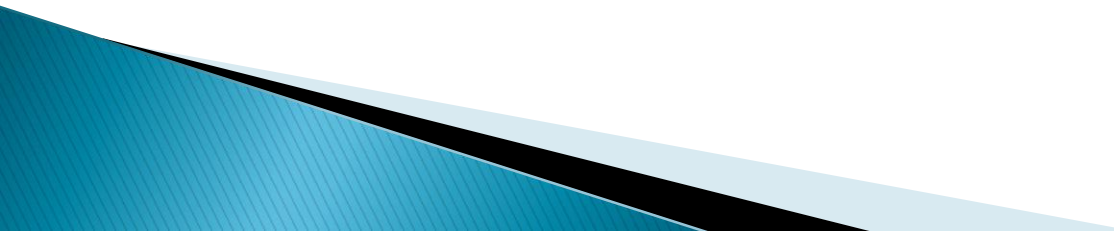


Indications for formal psychotherapy

Psychotherapy only if:

- Mild disorder.
- Psychotic or melancholic features are absent.
- History of chronic psychosocial problems.

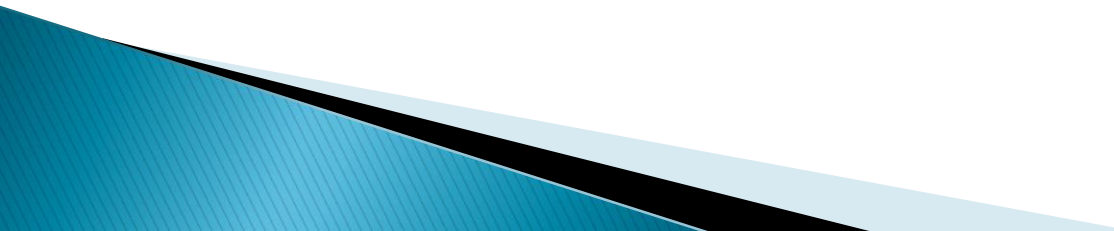
Indications for ECT

- Life-threatening depression
 - Inability to take medication
 - Contraindications to medication
 - Lack of response to medication
- 

Recurrence of depressive disorders

- 50% of patients with a major depressive disorder experience one episode
- 30% of patients become chronically depressed
- 20% of patients exhibit a recurrent course

Reasons for treatment of depression

- ▶ **Leads to high morbidity**
 - ▶ Increased loss of productivity / cost to national fiscus
 - ▶ **A painful illness**
 - ▶ Sometimes resistant to treatment
 - ▶ Family dysfunction
 - ▶ Substance abuse/ physical abuse
 - ▶ Conduct disorder
 - ▶ **Suicidal ideation, attempted/completed suicides**
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PATIENT HEALTH QUESTIONNAIRE 9 (PHQ9)

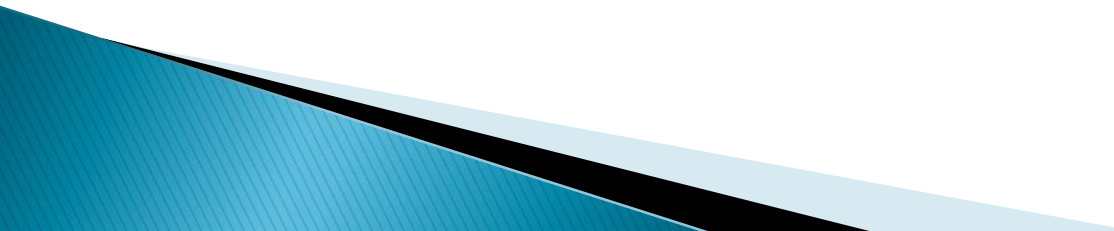
► *Over the last two weeks, how often (much) were you bothered by the following*

1. Little interest or pleasure in doing things 0 1 2 3
2. Feeling down, depressed, or hopeless 0 1 2 3
3. Trouble falling or staying asleep, or sleeping too much 0 1 2 3
4. Feeling tired or having little energy 0 1 2 3
5. Poor appetite or overeating 0 1 2 3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down 0 1 2 3
7. Trouble concentrating on things, such as reading the newspaper or watching television 0 1 2 3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual 0 1 2 3
9. Thoughts that you would be better off dead or of hurting yourself in some way 0 1 2 3

PHQ9 scoring

- ▶ FOR OFFICE CODING 0 + _____ + _____ + _____
- ▶ =Total Score: _____
- ▶ If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?
- ▶ Not difficult at all
- ▶ ☐
- ▶ Somewhat difficult
- ▶ ☐
- ▶ Very difficult
- ▶ ☐
- ▶ Extremely difficult
- ▶ ☐
- ▶ Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from
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Co-morbidities

- ▶ Conduct disorder – in adolescents and usually with atypical presentation
 - ▶ ADHD – with/without hyperactivity
 - ▶ Schizophrenia, Affective disorders, Anxiety, PTSD and so on
 - ▶ Substance Abuse – in adolescents and adults
 - ▶ Underlying medical conditions – chronic illnesses such as **CANCER, DIABETES, HIV/AIDS**
 - ▶ Prescribed medications e.g. **Methyldopa**
 - ▶ Stroke and post MI
 - ▶ Others such as MS, Hypertension etc.etc.
- 

Diabetes and
depression interact in
terms of prevention,
prevalence, risk factors,
clinical manifestations,
diagnosis and treatment

Definitions

- ▶ Response– when treatment of depression results in at least 50% improvement in symptoms
- ▶ Remission– when treatment results in removal of all symptoms for the first several months
- ▶ Recovery– if remission is sustained for longer than 6–12 months
- ▶ Relapse– when depression returns before there is full remission or within the first few months following remission
- ▶ Recurrence– when depression returns after a patient has recovered
- ▶ In clinical trials of AD Rx, the response rate is as follows:
 - 50–70% respond
 - **Up to 45% do not achieve remission**
 - **25–35% achieve full remission**
 - One third experience chronic symptoms – **but functional**
 - Half need ongoing Rx
 - Relapse occurred in 76% of pt's with residual symptoms (thus residual symptoms are a strong predictor of relapse)

Affective vs. Somatic Symptoms

▶ COGNITIVE/AFFECTIVE

- ▶ Depressed mood
- ▶ Loss of interest
- ▶ Guilt, worthlessness
- ▶ Hopelessness
- ▶ Suicidal ideation

▶ SOMATIC

- ▶ Appetite/Weight loss
- ▶ Sleep disturbance
- ▶ Agitation/retardation
- ▶ Fatigue

SCOTT R. PENZAK et al
2000

Treatment options

- ▶ SSRIs first line treatment
- ▶ TCAs can also be first line, but low doses may be insufficient and higher doses may cause interactions or toxicity; side-effects may be troublesome/complicate HIV disease

General Info

- ▶ Remission and recovery are the goals when treating depression
- ▶ All AD's have the same response rate: 67% respond to any given medication and 33% fail to respond within 8 weeks
- ▶ Depressed patients who have an initial treatment response will relapse at a rate of about 10–20% if the medication is continued for 6 months to a year following recovery
- ▶
- ▶ According to the STAR–D trial (sequenced treatment alternatives to relieve depression), one third of pt's will remit during Rx with any AD initially. In those who fail to remit, the likelihood of remission with another AD monotherapy goes down with each successive trial
- ▶ Adults between the ages of 25–65 have the best chance of getting a good response & having good tolerability to the AD
- ▶ The field of AD Rx is now moving to the use of as many mechanisms as necessary to gain remission; whether that means using 1 drug with multiple mechanisms or using several drugs, each with a different mechanism

Hypotheses on Depression

1. Monoamine hypothesis of depression:

- ▶ A deficiency in SA, NE &/ DA (monoamines) leads to depression, thus an increase in these neurotransmitters should result in return to a normal state. All AD's boost the synaptic action of 1/more of the monoamines, usually by blocking presynaptic transporters thereby increasing synaptic availability of the neurotransmitters & theoretically reducing symptoms of depression

2. Neurotransmitter receptor hypothesis of AD action:

- ▶ Depression is caused by upregulation of monoamine receptors, thus AD efficacy would be related to desensitization & downregulation of those receptors. The time taken for receptor adaptation to occur is the reason for the delayed onset of clinical effects as well as for development of tolerance to the drug's SE's

3. Monoamine hypothesis of AD action on gene expression:

- ▶ Adaptations in receptor number or sensitivity are due to alterations in gene expression

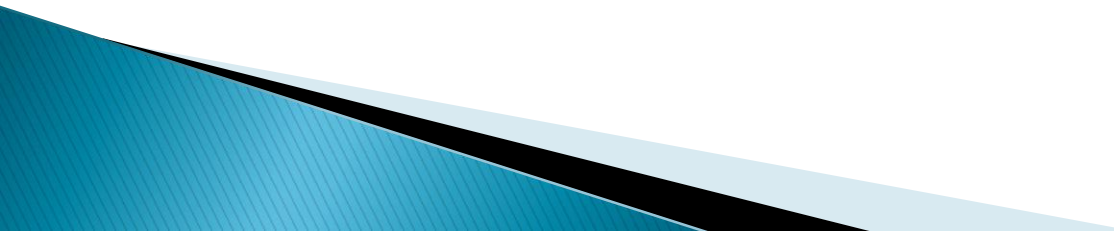
The neurobiological basis of depression

- ▶ Three classes of molecules are involved in depressive symptoms:
 1. Monoamines: regulate broad functioning of neural circuits
 2. Neuropeptides: mediate behavior specific components of neural circuits e.g. hypocretin
 3. **Neurotrophins– allow for plasticity of the brain & maintenance of neural circuits e.g. brain derived neurotrophic factor (BDNF).**
Chen et al. reported results from a postmortem study that found increased BDNF expression in pt's who had been treated with AD's
- ▶ Changes in pathophysiology seen with AD Rx:
 1. Normalization in NE & SA regulation
 2. Increase in BDNF levels
 3. Increase in hippocampal size
- ▶ a study by Avissar et al. suggest that B-arrestin-1 levels in pt's with depression may potentially serve as a biochemical marker for depression.


How to choose an AD

- ▶ First line monotherapy– SSRI's, NDRI's, SNRI's
- ▶ Second line monotherapy– alpha2 antagonists, NRI's, TCA's, SARI's, MAOI's
- ▶ Augmenting agents– hypnotics, 5HT1A agonists, lithium, **BZ's**, modafinil, DA partial agonists (DPA's), folate, thyroid H, stimulants, light therapy (Benedetti et al. showed that the combo of citalopram & light treatment was more effective than citalopram & placebo in the Rx of MDD. Low intensity light Rx hastened & potentiated the effect of citalopram, thus providing the possibility of an augmenting strategy that's devoid of SE)
- ▶ Ancillary treatments– CBT/IPT, ECT, VNS, DBS, rTMS


Strategies to enhance the chances of achieving remission in depression:

- ▶ Psychoeducation
 - ▶ Enhance compliance
 - ▶ Optimal dosing
 - ▶ Optimal duration of Rx (continuing AD's for 4–9 months after the remission of acute symptoms has been demonstrated to reduce the risk of relapse or recurrence; & the general consensus recommends the use of AD's for at least one year after full remission)
 - ▶ Address residual symptoms & SE
- 

Psychotic depression

- ▶ TCA's are more effective than newer AD's for psychotic depression, but the response rate is poorer than for non psychotic depression
 - ▶ A combo of an AD & an antipsychotic is more effective than an antipsychotic alone but it is not clear if it is more effective than an AD alone
 - ▶ Response rates of 64% for olanzapine–fluoxetine combo
 - ▶ Is an indication for ECT
 - ▶ Potential use of glucocorticoid R' antagonist mifepristone (still under experiment)
- 


SSRI's & bleeding

- ▶ SSRI's inhibit the SA transporter which is responsible for the uptake of SA into platelets. It may thus be predicted that SSRI's will deplete platelet SA, leading to a reduced ability to form clots & a subsequent increase in the risk of bleeding.
 - ▶ Database studies have found that pt's who take SSRI's are at 3 fold increased risk of being admitted to hosp with an upper GI bleed
 - ▶ The elderly & those with a hx of previous GI bleed are at increased risk
 - ▶ There is also increased risk of lower GI bleeding & uterine bleeding
 - ▶ Gastro-protective agents should be considered on those pt's taking SSRI's that have other risk factors for bleeding (e.g. aspirin use)
 - ▶ Studies have failed to find a reduction in the risk of ischaemic stroke, or increase in the risk of haemorrhagic stroke in SSRI users
 - ▶ Other studies suggest that SSRI's have a very low rate of cerebrovasculature adverse reaction, however pharmacovigilance is required for Rx of pt's with high risk for bleeding & stroke
- 

AD's & diabetes mellitus

- ▶ Presence of depression has a negative impact on metabolic control & likewise poor metabolic control may worsen depression
- ▶ All pt's diagnosed with depression must be screened for DM
- ▶ Pt's with MDD & DM should be treated with SSRI's (fluoxetine), avoid TCA's & MAOI's
- ▶ A study in middle aged Finnish pt's over a 7 year period found a 2 fold increase in the risk of depression in pt's with metabolic syndrome compared with those without, & lipid levels were the most NB factor in this increased risk. These findings suggest that metabolic syndrome precedes the onset of depression, due to possible insulin resistance leading to increased cortisol, or decreased serotonergic activity or psychological factors related to body image. The Rx of metabolic syn. may therefore be another target for preventing depressive episodes & the findings also have wider implications for the use of atypical antipsychotics in the Rx of depression

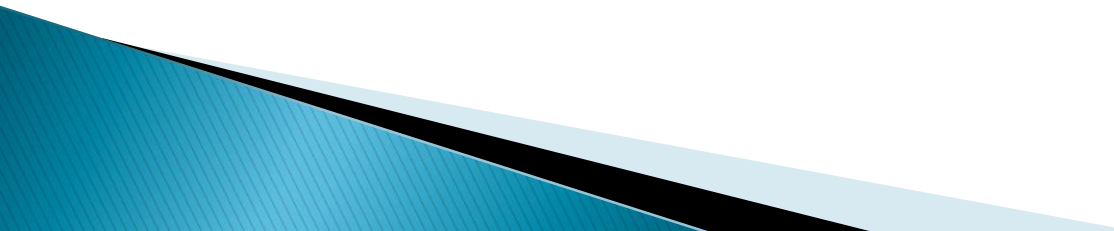
AD's & diabetes mellitus cont.

- ▶ Taking moderate to high daily doses of AD'S for >2 years is associated with an 84% increased risk for DM, according to a large observational study (particularly with paroxetine & amitriptyline)
 - ▶ Weight gain might explain much of the relation between antidepressant use and diabetes
 - ▶ For patients needing long-term treatment with antidepressants, compliance with lifestyle recommendations is recommended to prevent diabetes
 - ▶ Other than weight gain, mechanisms leading to increased risk for diabetes could include the hyperglycemic effects of noradrenergic activity of antidepressants. Depression itself might increase the risk for diabetes. Research shows that patients with depression have a 35% higher risk of developing diabetes than non-depressed people.
 - ▶ If a patient who has responded well to amitriptyline in the past presents again with severe depressive episode, anti-depressive effectiveness might outweigh an increased risk of diabetes
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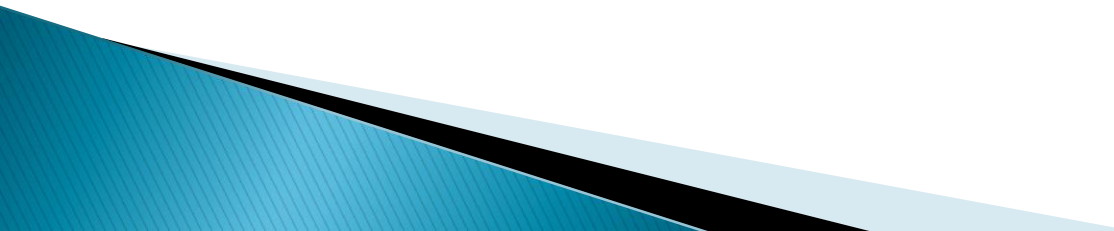
AD's & suicide risk

- ▶ Pt's with MDD are at greater risk of suicide, hence the APA guideline urges that pt's be assessed for suicide risk initially and over the course of Rx, since suicide risk in some pt's recovering from MDD increases transiently as they develop the energy and capacity to act on self-destructive plans
- ▶ Recent research has raised concern about the safety of AD use for children and adolescents and has led the FDA to add additional warnings to the labeling of all AD medications
- ▶ In 23 short-term trials of 4,400 pt's receiving 9 AD drugs (SSRIs & others), suicidal thinking/behavior was observed in 78 pt's. Average risk of suicidal thinking/behaviors was 3.8% for participants receiving a drug compared to 2.1% for those given placebo, suggesting a 2 fold increase in risk with AD's
- ▶ APA suggests that prescriptions be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose & that pt's be screened for bipolar d/o before AD Rx is initiated
- ▶ Studies by Grunebaum et al. in 2004 showed that there has been a decline in the suicide rate in the USA from 1985–1999 due to a greater proportion of mood disorders being treated with SSRI's & other 2nd generation non tricyclic AD's

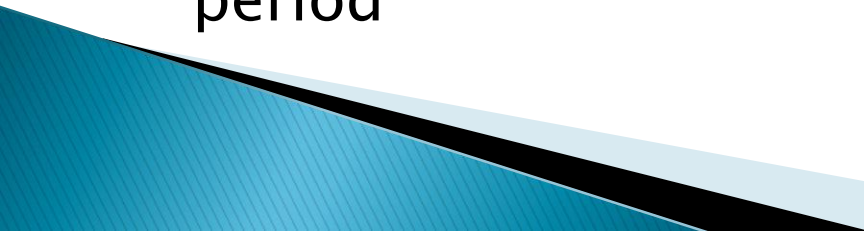
AD's & sexual dysfunction

- ▶ Both depression & AD's can cause sexual dysfunction
 - ▶ Treated by dose reduction or drug switching
 - ▶ Bupropion has the lowest risk of sexual dysfunction. Mirtazapine is also favoured
 - ▶ Addition of sildenafil, tadalafil or bupropion may improve sexual function
- 

AD's & hepatotoxicity

- ▶ The reported incidence of hepatic adverse reactions to nefazodone seems to be higher than that estimated so far. Nefazodone has the highest incidence of hepatotoxicity. Given the high prevalence of depression and the widespread use of AD's, Dr's should be alert to the possibility that these medications cause hepatitis and consider early discontinuation of an AD if the condition is suspected
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Swapping & stopping AD's

- ▶ Be wary of “discontinuation” symptoms (esp if on Rx for >6 weeks, or treated with paroxetine/venlafaxine)= R' rebound= affective, GIT, neuromotor, vasomotor or neurosensory symptoms (can be mistaken for relapse or for a new physical illness). Are common in neonates born to women taking AD's
 - ▶ Cross tapering is preferred, while monitoring tolerability
 - ▶ Cross tapering may not be necessary in some cases e.g. switching SSRI's
 - ▶ Potential dangers of cross tapering= serotonin syndrome!!!
 - ▶ AD's should be discontinued over at least a 4 week period
- 

CONCLUSION

- ▶ Diagnose depression carefully
 - ▶ Use rating scales if possible
 - ▶ May have to get assistance from psychologist
 - ▶ Inform patient about the treatment plan
 - ▶ Insist on adherence to treatment
 - ▶ Choose AD carefully
 - ▶ Start low and increase on weekly basis
 - ▶ Listen to the patient and give assurance but switch if problem persists
 - ▶ DO suicide risk assessment – Admit if positive
 - ▶ Use a screening instrument such as PHQ 9
- 