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General Adult

Depression 3 (Semester 3)

Developing people for health and healthcare

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Aims and Objectives

- To develop an understanding of the bio-psychosocial management of Depression.
- To develop an understanding of evidence based treatment.

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Expert Led Session

Depression

Biopsychosocial management and evidence-based treatment

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Outline

- NICE guidelines
- Antidepressants
- Treatment Resistant Depression
- CBT & MCBT
- IPT
- Evidence Base for the above treatments

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NICE Guidelines
Principles for assessment

- When assessing a person who may have depression, conduct a comprehensive assessment that does not rely simply on a symptom count.

- Take into account:
  - the degree of functional impairment and/or disability associated with the possible depression **and**
  - the duration of the episode.

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NICE-The stepped-care model

Focus of the intervention	Nature of the intervention
STEP 4: Severe and complex[1] depression; risk to life; severe self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care
STEP 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high-intensity psychological interventions, combined treatments, collaborative care[2], and referral for further assessment and interventions
STEP 2: Persistent subthreshold depressive symptoms; mild to moderate depression	Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions
STEP 1: All known and suspected presentations of depression	Assessment, support, psycho-education, active monitoring and referral for further assessment and interventions

[1,2] see slide notes

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Step 2 –
Low-intensity psychosocial treatments

- For people with persistent subthreshold depressive symptoms or mild to moderate depression,
  - individual guided self-help based on the principles of cognitive behavioural therapy (CBT)
  - computerised cognitive behavioural therapy (CCBT)
  - a structured group physical activity programme.

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Step 3 –
Drug treatment –NICE guideline

- Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor

- For people with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention (cognitive behavioural therapy [CBT] or interpersonal therapy [IPT]).

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Antidepressants

All medications have essentially equivalent efficacy

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Tricyclic Antidepressants (TCAs)

Characteristic three-ring nucleus	
Biochemical effects	"Tertiary" TCAs (Amitriptyline, Chlomipramine, Imipramine) - Inhibit 5-HT uptake + weaker inhibition of NE uptake "Secondary" TCAs (Desipramine, Nortriptyline) - Inhibit NE uptake + weaker inhibition of 5-HT uptake
Temporal delay of weeks for clinical effects,	although biochemical effects are immediate

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Tricyclic Antidepressants (TCAs)

Neuropharmacology

- Inhibit monoamine uptake (NE and 5-HT)
- Muscarinic cholinergic antagonism
- H_1 histamine antagonism
- α_1-adrenergic antagonism

Side effects

- Dry mouth
- Constipation
- Dizziness
- Tachycardia
- Urinary retention
- Impaired sexual function
- Orthostatic hypotension

Tricyclic Antidepressants (TCAs)

Contraindications

- QTc greater than 450 msec
- Conditions worsened by muscarinic blockade (eg myasthenia gravis, BPH)
- pre-existing orthostatic hypotension
- Seizure disorder

Complications

- Cardiotoxicity: resulting from combination of:
  - Conduction defects, arrhythmias
- Delirium
- Potentiation of effects of other sedating drugs

Monoamine Oxidase Inhibitors (MAOIs)

- Irreversibly inhibit monoamine oxidase enzymes
- Effective for major depression, panic disorder, social phobia
- Drug interactions and dietary restrictions limit use

- Occurs as two isoenzymes
    - MAO-A – Oxidizes norepinephrine, serotonin, tyramine
    - MAO-B - selective for dopamine metabolism

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MAOIs - Dietary and Drug Interactions

- Increased stores of catecholamines sensitize patients to effects of sympathomimetics
- Accumulation of tyramine (sympathomimetic) = high risk of hypertensive reactions to dietary tyramine
  - requires dietary restrictions
- Interactions with other sympathomimetic drugs
  - Antidepressants
  - OTC cold remedies
    - phenylpropanolamine
  - Meperidine
  - L-dopa

Examples of MAOIs

- Irreversible, non-selective MAOIs
  - phenelzine
  - isocarboxazid
  - tranylcypromine

- Selective MAO-B inhibitors
  - deprenyl (selegiline)
  - loses its specificity for MAO-B in antidepressant doses

- Reversible monoamine oxidase inhibitors (RIMAs)
  - Moclobemide
  - Appears to be relatively free of food/drug interactions

Selective Serotonin Uptake Inhibitors (SSRIs)

- Currently marketed medications
  - Fluoxetine (Prozac).
  - Sertraline (Lustral).
  - Paroxetine (Seroxat)
  - Fluvoxamine (Luvox)
  - Citalopram (Cipramil)
  - Escitalopram (Cipralex)

- Selectively inhibit 5-HT (not NE) uptake
- Differ from TCAs by having little affinity for muscarinic, as well as many other neuroreceptors

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Much higher therapeutic index than TCAs or MAO-I's
- Much better tolerated in early therapy
- Equal or almost equal in efficacy to TCAs

Side effects

- Nausea
- Sexual dysfunction
  - Delayed ejaculation/anorgasmia
- Anxiety
- Insomnia
- Hyponatremia

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Serotonin syndrome

- Evoked by interaction between serotonergic agents
  - e.g., SSRIs and MAOIs
  - Combination of increased stores plus inhibition of reuptake after release
- Symptoms
  - Hyperthermia
  - Muscle rigidity
  - Myoclonus
  - Rapid changes in mental status and vital signs
- Can be fatal

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SNRIs - Selective Norepinephrine-Serotonin Reuptake Inhibitors

- **Venlafaxine (Effexor), Duloxetine (Cymbalta),**
  - relatively devoid of antihistaminergic, anticholinergic, and antiadrenergic properties
  - nonselective inhibitor of both NE and 5-HT uptake.

Side effects:

GI , Sexual dysfunction, hypertension (venlafaxine), hyponatremia

Other antidepressants

- Trazodone
  - mixed 5-HT agonist/antagonist
    - α_1 antagonist
    - H_1 antagonist
- Nefazodone (Serzone)
  - 5 HT_2 antagonist

- Bupropion (Wellbutrin; Zyban)
  - Inhibits uptake of DA and NE
  - antismoking properties probably involves parent molecule
  - Lacks sexual side effects
  - Seizure risk

- Mirtazapine
  - α_2 antagonist
  - $5H_2$ and $5HT_3$ antagonist
  - Net effect selective increase in $5HT_{1A}$ function
  - H_1 antagonist

  - advantages: sedation, no adverse sexual effects

- Vortioxetine (Brintellix, Trintellix)

- Serotonin reuptake inhibitor
- 5HT1A partial agonist
- 5HT3 receptor antagonist

Recommended by NICE after 2 failed trials of antidepressants

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A Working Definition of Treatment Resistant Depression

6-8 weeks of at least a middle range dose without remission

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TRD-Strategies (as per Maudsley guidelines)

Level 1	Initial Treatment: Citalopram
Level 2	Switch To: bupropion, sertraline, Venlafaxine
	Augment With: bupropion, buspirone
Level 3	Switch To: mirtazapine or nortriptyline
	Augment With: Lithium or T3
Level 4	Switch To: Tranylcypromine or mirtazapine combined with venlafaxine

ECT should be considered at all stages if indicated.

- Patients suffering from major depression (primarily with chronic disease and multiple recurrences) in Primary and Specialty Care settings have a 30% chance of achieving full remission with an adequate dose of Citalopram

- Patients who did not remit with citalopram had a 1 in 4 chance of achieving remission by switching to bupropion, sertraline or venlafaxine and a 1 in 3 chance of responding to augmentation of the citalopram with bupropion or buspirone

- Depressed patients who fail to respond to two antidepressant trials are have a 12-20% remission rate with another single antidepressant agent and a 16-25% remission rate with T3 or lithium augmentation

Electroconvulsive Therapy

- Response rate in patients with
  - inadequate medication trials: 86%
  - adequate trials: 50%

- Probably treatment of choice for catatonic states

- Relapse rate of 50% without out relapse prevention medication – Li best evidence for relapse prevention

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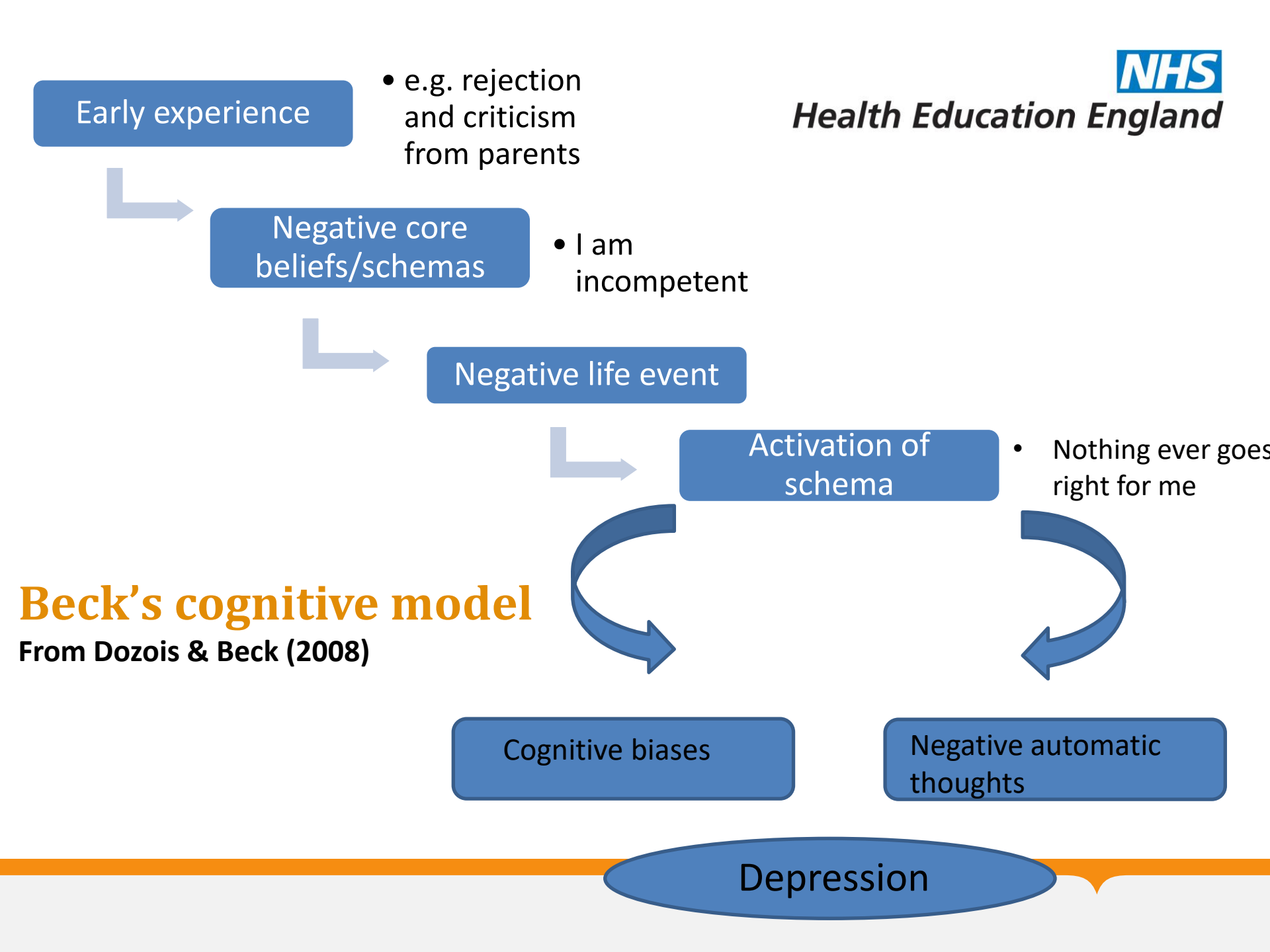
Cognitive Behavioural Therapy (CBT)

- One of the most extensively researched forms of psychotherapy with over 325 outcome studies looking at CBT effectiveness published in 2006 (Butler et al., 2006).

- CBT encompasses a number of therapeutic cognitive and behavioural approaches. The compelling evidence base for CBT lead to an announcement in 2007 that there would be £173 million into an Improving Access to Psychological Therapies Program (IAPT) based on the finding that CBTs were more efficient than pharmacotherapy or other interventions (Rachman & Wilson, 2008).



Beck's cognitive model

From Dozois & Beck (2008)

CBT STRUCTURE

Structured:
- Time limited
- Problem orientated

Role of therapist:
- As a guide
- As a scientist practitioner
- Socratic method

Cognitive techniques:
- Hot cognitions

Recording cognitions (mood diaries)
- Identifying cognitive biases

Behavioural techniques:
- Behavioural experiments
- Experiments with therapist
- Experiments alone

From: Westbrook, Kennerley, & Kirk (2007)

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Efficacy of CBT for depression

- Based on clinical trials evidence – NICE recommends CBT for depression http://www.nice.org.uk/cg90
- CBT is more effective than no intervention
  - Based on meta-analysis of 97 studies, d = 0.67, Cuijpers et al., 2011
- Is equally effective as other types of psychological therapy
  - Based on meta-analysis of 56 studies, d = 0.03, Cuijpers et al., 2011
- CBT is equally effective to antidepressant medication, and may be more effective at preventing relapse (De Rubeis et al., 2005)

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Mindfulness Based Cognitive Therapy (MBCT)

- MBCT aims to prevent depressive relapse by developing awareness of and changing the relationship with unwanted negative thoughts, feelings and bodily sensations.

- In this way previously depressed individuals respond to negative thoughts not in an automatic way, but in a skilful intentional way.

Ma & Teasdale (2004)

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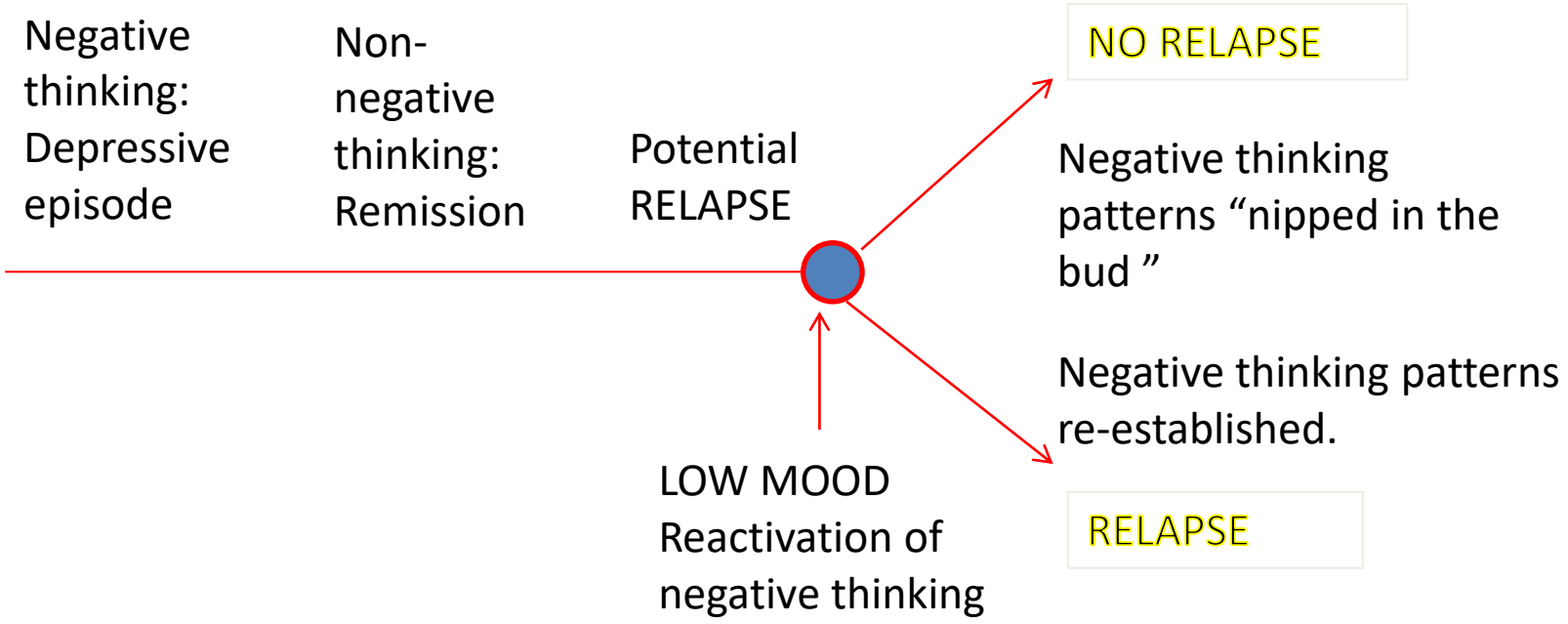
Core assumptions of MBCT

MBCT assumes that once in a mode of recovery from depression, previously depressed individuals will still be vulnerable to experiencing low mood and patterns of negative thinking.

Model underlying development of MBCT for depressive relapse



From: Segal, Williams, & Teasdale (2002), p. 37

Comparing MBCT and CBT

- Practical differences:
  MBCT delivered in a group format whereas CBT is often 1:1
  MBCT is based on an 8 week program
- Theoretical differences:
  - CBT encourages individuals to identify and change maladaptive thoughts by challenging the accuracy of their beliefs.
  - MBCT teaches individuals to recognise the occurrence of depressive thoughts without emotionally responding to them.

(Manicavasgar, Parker, & Perich, 2011)

- MBCT includes techniques and exercises from cognitive behavioural therapy with additional meditation components.

(Segal, Williams, & Teasdale, 2002)

- Both MBCT and CBT include didactic elements, which provides the participants with information about depression to facilitate them in recognising and dealing with their relapse signatures.

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Interpersonal Psychotherapy

Historical Influences of IPT

- Psychoanalysis
- Harry Stack Sullivan
- Object Relations Therapy
- Interpersonal Theory (Leary, Kiesler)

Roots in Psychodynamic Theory

- Primary instincts of sex and aggression involve relating to others
- Relationships with others contribute to personality development
- Psychological Problems due to deficits in early relations

➢Transference and counter-transference are interpersonal

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Outline of IPT Intervention

Initial Sessions (Overview)

- Assess Depressive symptoms
- Complete Interpersonal Assessment
- Identify Major Interpersonal Problem Area
- Explain IPT and make treatment contract

IPT designed for symptom reduction and improved interpersonal relationships

Focus on current disputes, frustrations, anxieties in the interpersonal context which impact mood and self esteem

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- Fava M, Rush AJ, Wisniewski SR, et al. A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients: A STAR*D Report. Am J Psychiatry 2006; 163:1161-1172.
- Nierenberg AA, Fava M, Trivedi MH, et al. A Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report. Am J Psychiatry 2006; 163:1519-1530.
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MCQ 1Q

1. **Which of the following neurotransmitters does Duloxetine act on?**

A. Serotonin only
B. Noradrenaline and Serotonin
C. Dopamine
D. Noradrenaline, Serotonin and Dopamine
E. GABA

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MCQ 1A

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C. Dopamine
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E. GABA

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MCQ 2Q

2. **Which of the following statements about Trazodone is FALSE?**

A. It is relatively safe in overdose
B. It does not have strong antihistamine properties
C. It is not a MAO-A and MAO- B inhibitor
D. It does not block 5-HT reuptake
E. It is a 5HT2 agonist

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MCQ 2A

2. **Which of the following statements about Trazodone is FALSE?**

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MCQ 3A

3. **Which of the following are not common side effects of mirtazapine?**

A. Sedation
B. Nausea, vomiting, abdominal pain
C. Sexual dysfunction
D. Agitation, anxiety
E. Increase appetite

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MCQ 3A

3. **Which of the following are not common side effects of mirtazapine?**

A. Sedation
B. Nausea, vomiting, abdominal pain
C. Sexual dysfunction
D. Agitation, anxiety
E. Increase appetite .

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MCQ

4. Laura is a depressed 61-year-old woman who has not responded to an SSRI and has urinary incontinence. Which one of the following antidepressants is the best choice in this situation?

A. Phenelzine
B. Mirtazapine
C. Vortioxetine
D. Trazodone
E. Duloxetine

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MCQ

The correct answer is: E. Duloxetine

- Explanation: In the BNF, Duloxetine is also licensed for urinary incontinence.
- Duloxetine is licensed for the treatment of major depressive disorder, which is an inhibitor of serotonin and noradrenaline re-uptake. It is licensed for the treatment of moderate to severe stress incontinence in women.

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MCQ 5Q

5. Hypertension is a common side effect of which of the following antidepressants?

A. Venlafaxine
B. Paroxetine
C. Escitalopram
D. Trazodone
E. Mirtazapine

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MCQ 5Q

A. Venlafaxine

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Any Questions?

Thank you.