Meet the Big 21 from the Largest Ever Study on Antidepressants – Mechanisms of Actions, Side effects and Indications

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The recent Cipriani et al. systematic review and network meta-analysis is the largest and most comprehensive examination of antidepressant efficacy and tolerability. The network meta-analysis (NMA) covered an extensive list of 21 antidepressants and placebo which included a total of 116477 patients in 522 double-blind, parallel RCT's. [1]

This article aims to provide a reader with a summary of the antidepressants featured in the NMA that should help with the individualised choice of antidepressant therapy by taking into account clinical features and tolerability.

The antidepressants have been divided into first and second line based on the recent RANZCP guidelines. [2]

It is important to recognise that according to the guidelines there is some flexibility regarding 1st, 2nd, and 3rd treatment, based on patient's symptoms. e.g Duloxetine may be a 1st line in a patient with depression and pain. SNRIs have been positioned as the 2nd line only because of more significant toxicity in overdose.

SNRI's and TCA's are more effective than SSRI's in treating severe depressive symptoms (HAM-D > 25) and melancholic depression and hence may be prescribed first line in these situations.

The antidepressants have been arranged in alphabetical order.

1. AGOMELATINE

Need to know:

- Dose – 25-50 mg nocte
- Metabolised by CYP1A2 – therefore inhibitors like fluvoxamine and ciprofloxacin are contraindications
- Monitor Liver function tests at 3,6,12 and 24 weeks. Discontinue if ALT or AST exceed 3 times normal range.

- We covered a detailed summary of agomelatine previously in https://psychscenehub.com/psychinsights/agomelatine-mechanism-action/
- Read about the use of agomelatine in a clinical case of depression in https://psychscenehub.com/psychinsights/depression-and-ocd-treatment/

Agomelatine
1st line (RANZCP guidelines)

Antidepressant class
Melatonergic agonist

Principal mechanism of action
Melatonin agonist (M1 & 2 receptors) and 5-HT2C antagonist (Increases frontal dopamine).

Prescribed for the following features of depression:
Sleep problems, sexual dysfunction, poor hedonic drive.

2. AMITRYPTILINE

Need to know:

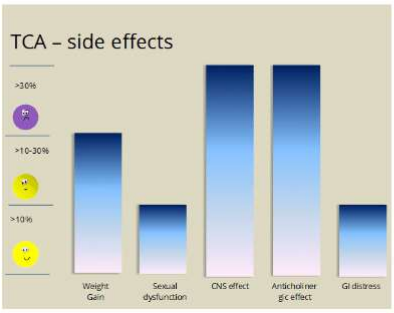
- Effective antidepressant but limited by its tolerability profile.
- Anti-H1 action leads to weight gain; Anticholinergic action leads to dry mouth, constipation, blurred vision and urinary retention; Alpha-1 antagonism leads to orthostatic hypotension and dizziness; Voltage-sensitive sodium channel (VSSC) blockade leads to arrhythmias, coma and seizures in overdose.
- Dose – 50-200 mg nocte
- Effective at low doses 25-50 mg nocte for neuropathic pain.
- Risk of serotonin syndrome when combined with SSRI's or SNRI's.
- Half life- 18-96 hours.

Amitriptyline
2nd line (RANZCP Guidelines)

Antidepressant class
Tricyclic Antidepressant (TCA)

Principal mechanism of action
Block NA reuptake. Inhibits H1, Alpha-1, & M1 receptors. Broad spectrum of actions, including blockade of voltage-sensitive Na channels.

Prescribed for the following features of depression:
Pain and Melancholia



3. BUPROPION

Need to know:

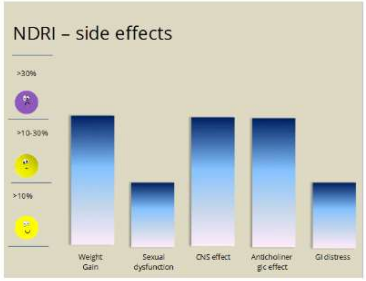
- Blocks Dopamine transporters (DAT's) in nucleus accumbens and striatum increasing dopamine in these areas which improves 'positive affect'. Learn more about positive affect in a talk by Prof Malcolm Hopwood at https://psychscenehub.com/video/899/
- Dose- 150-450 mg/day
- Available in immediate release (IR) and extended release (XL)
- Metabolised by CYP2B6 into many active metabolites
- Inhibits CYP2D6
- A half life of 21-30 hours
- Reduces seizure threshold
- Common side effects are dry mouth, insomnia and nausea

Bupropion
1st line (RANZCP Guidelines)

Antidepressant class
Noradrenaline-Dopamine Reuptake Inhibitors (NDRI)

Principal mechanism of action
Blocks the action of the noradrenaline transporter and dopamine transporter thus increasing Noradrenaline (NA) and Dopamine (DA).

Prescribed for the following features of depression:
Fatigue



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4. CITALOPRAM

Need to know:

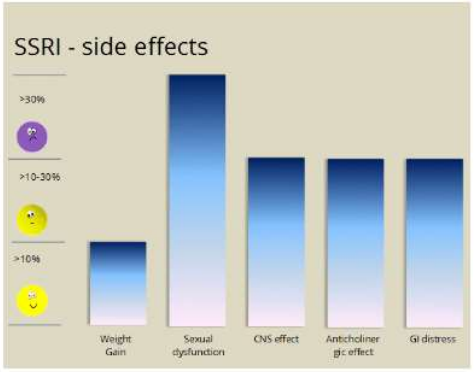
- SSRI with good and bad enantiomer (R and S)
- R-enantiomer has mild antihistaminic properties
- Dose – 20-80 mg /day. (The higher doses are prescribed in OCD)
- Dose-dependent QTc prolongation
- Not a potent CYP inhibitor
- A half-life of 24-72 hours.
- SSRI's as a group can be associated with GI bleeding and hyponatraemia in the elderly

Citalopram
1st line (RANZCP Guidelines)

Antidepressant class
Selective Serotonin Reuptake Inhibitor (SSRI)

Principal mechanism of action
Selective 5-HT reuptake blockade.

Prescribed for the following features of depression:
Anxiety



5. CLOMIPRAMINE

Need to know:

- Tricyclic with selective serotonin reuptake inhibition
- Dose- 25-250 mg/day
- Second line after SSRI's in OCD
- Half-life is 12-26 hours
- Side effects are similar to amitryptiline due to its H1, Alpha1 and VSSC antagonism.

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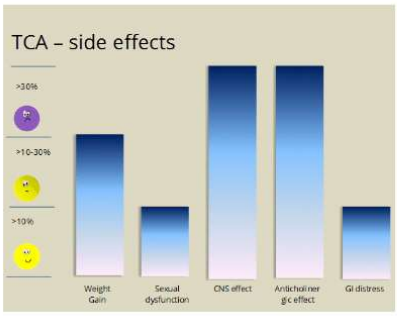
Clomipramine
2nd line (RANZCP Guidelines)

Antidepressant class
Tricyclic Antidepressant (TCA)

Principal mechanism of action
Selective 5HT reuptake inhibitor. Inhibits H1, Alpha 1, & M1 receptors. Broad spectrum of actions, including blockade of voltage-sensitive sodium channels.

Prescribed for the following features of depression:
Pain, Melancholia, OCD



6. DESVENLAFAXINE

Need to know:

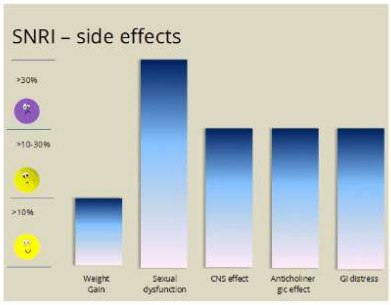
- The active metabolite of Venlafaxine
- Greater Noradrenergic transporter (NAT) inhibition than Serotonin transporter (SERT) inhibition compared to venlafaxine
- Dose – 50-150 mg /day
- Not metabolised by CYP2D6, therefore, no significant variation in serum levels of the active metabolite
- Can reduce vasomotor symptoms in perimenopausal women.
- Can be used in liver dysfunction as not metabolised by the liver

Desvenlafaxine
2nd line (RANZCP Guidelines)

Antidepressant class
Serotonin and Noradrenaline Reuptake Inhibitor (SNRI). Desvenlafaxine is a metabolite of Venlafaxine.

Principal mechanism of action
Block both serotonergic and nonradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.

Prescribed for the following features of depression:
Melancholia: severe depression.



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7. DULOXETINE

Need to know:

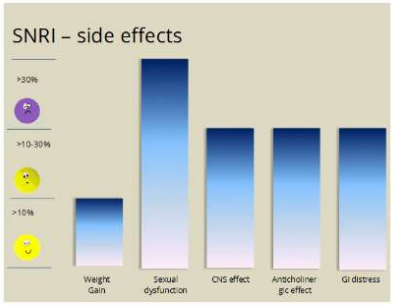
- Specifically indicated in pain with depression. Can improve diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain
- Milder withdrawal reaction and lower incidence of hypertension as compared to Venlafaxine
- Dose – 60-120 mg /day. Can be administered twice a day
- Half-life is 12 hours

Duloxetine
2nd line (RANZCP Guidelines)

Antidepressant class
Serotonin and Noradrenaline Reuptake Inhibitor (SNRI)

Principal mechanism of action
Block both serotonergic and nonradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.

Prescribed for the following features of depression:
Severe Depression, Pain.



8. ESCITALOPRAM

Need to know:

- S-enantiomer of citalopram which makes escitalopram the best-tolerated SSRI
- Dose 10-40 mg/day (The higher dose is prescribed in OCD)
- A propensity for QTc prolongation which is dose-dependent
- No significant CYP enzyme interactions

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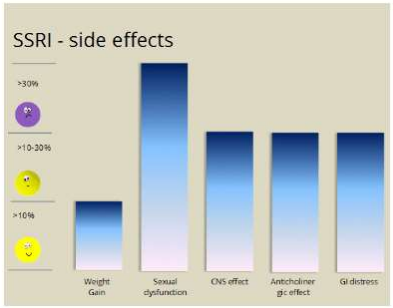
Escitalopram
1st line (RANZCP Guidelines)

Antidepressant class
Selective Serotonin Reuptake Inhibitor (SSRI)

Principal mechanism of action
Selective 5-HT reuptake blockade. S-enantiomer of Citalopram

Prescribed for the following features of depression:
Anxiety



9. FLUOXETINE

Need to know:

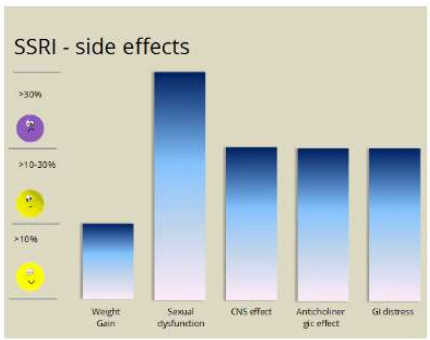
- SSRI with 5HT2C antagonism. (More discussion about 5HT2C antagonism in the article on agomelatine at https://psychscenehub.com/psychinsights/agomelatine-mechanism-action/)
- 5HT2C antagonism increases pre-frontal dopamine which may be activating for some patients; however, may benefit patients with lack of motivation and anhedonia
- Dose – 20-60mg/day
- Inhibits CYP2D6 and CYP3A4. (can increase levels of risperidone, diazepam)
- Long half-life (2-3 days) with its active metabolite having a half-life of 7-14 days

Fluoxetine
1st line (RANZCP Guidelines)

Antidepressant class
SSRI

Principal mechanism of action
Selective 5-HT reuptake blockade.

Prescribed for the following features of depression:
Anxiety



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10. FLUVOXAMINE

Need to know:

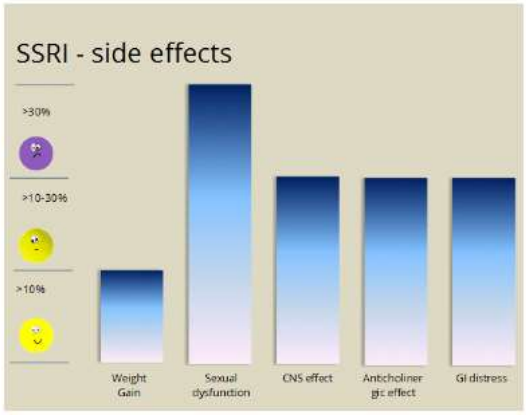
- SSRI with sigma(σ)1 binding properties which may contribute to anti-anxiety and antipsychotic properties
- Dose – 100-300 mg /day (The higher doses are used in OCD)
- CYP1A2/CYP2C19/CYP3A4 inhibitor- can increase levels of olanzapine and clozapine (CYP1A2), methadone, benzodiazepines and carbamazepine (CYP3A4)
- Half life – 24-72 hours

Fluvoxamine
1st line

Antidepressant class
SSRI

Principal mechanism of action
Selective 5-HT reuptake blockade.

Prescribed for the following features of depression:
Anxiety



11. MILNACIPRAN AND 12. LEVOMILNACIPRAN

Need to know:

- More potent noradrenaline transporter inhibitor (NAT) than SERT inhibitor
- Dosed twice daily due to a short half-life of 6-8 hours
- Dose 50-100mg BD
- Minimal CYP metabolism

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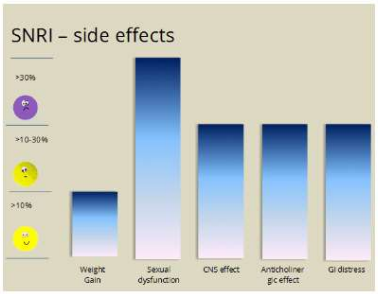
Milnacipran and Levomilnacipran
2nd line

Antidepressant class
SNRI. Levomilnacipran is an active enantiomer of the racemic drug milnacipran.

Principal mechanism of action
Block both serotonergic and nonradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.

Prescribed for the following features of depression:
Co-Morbid Fibromyalgia



13. MIRTAZAPINE

Need to know:

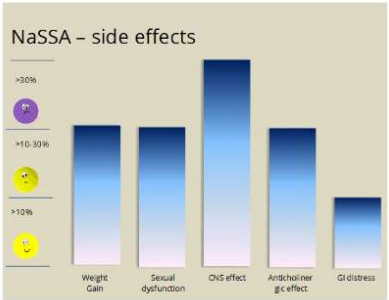
- Mirtazapine works through α2 pre-synaptic antagonism and 5HT2A, 5HT2C, 5HT3 and H1 antagonism
- Alpha 2 antagonism increases serotonin and noradrenaline release
- Combined use with SNRI's is termed as california rocket fuel due to its significant NA and DA increasing properties
- Dose 15-60 mg/day
- Lower doses have a sedating property due to greater anti-histaminic effects which is also responsible for weight gaining properties.

Mirtazapine
1st line (RANZCP Guidelines)

Antidepressant class
Noradrenergic and Specific Serotonergic Antagonist (NaSSA)

Principal mechanism of action
Blocks Alpha 2 pre-synaptic receptors (increasing noradrenaline and dopamine in prefrontal cortex). 5HT2A and 5HT2C antagonist.

Prescribed for the following features of depression:
Insomnia, circadian rhythm disruption, weight loss, reduced appetite



14. PAROXETINE

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Need to know:

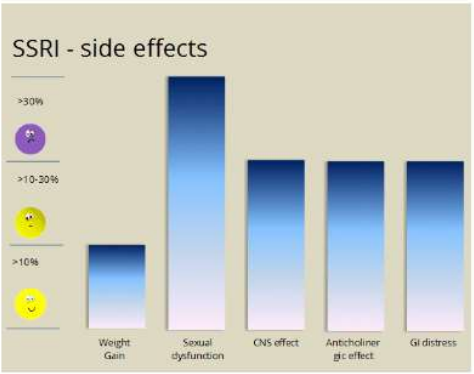
- SSRI with muscarinic anticholinergic and noradrenaline transporter (NAT) inhibitory actions
- More calming and sedating than other SSRI's
- Greater discontinuation symptoms contributed by additional anticholinergic withdrawal
- Dose – 20-60 mg/day
- Inhibitor of CYP2D6 and CYP3A4
- Half life -24 hours

Paroxetine
1st line (RANZCP Guidelines)

Antidepressant class
SSRI

Principal mechanism of action
Selective 5-HT reuptake blockade

Prescribed for the following features of depression:
Anxiety



15. REBOXETINE

Need to know:

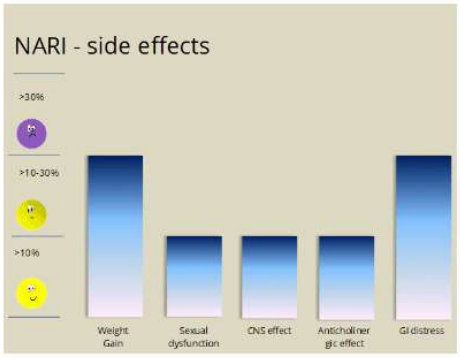
- Dose – 8-12 mg/day (administered twice a day)
- Metabolised by CYP3A4 (avoid ketoconazole and erythromycin)
- Half life -13 hours
- Common side effects include insomnia, fatigue, nausea, dry mouth and constipation

Reboxetine
1st line (RANZCP Guidelines)

Antidepressant class
Noradrenaline reuptake inhibitor (NARI)

Principal mechanism of action
Reuptake inhibitor for noradrenaline and adrenaline.

Prescribed for the following features of depression:
When activation is necessary (e.g. amotivation & withdrawal).



16. SERTRALINE

Need to know:

- SSRI with DAT inhibition and sigma(σ)1 binding properties

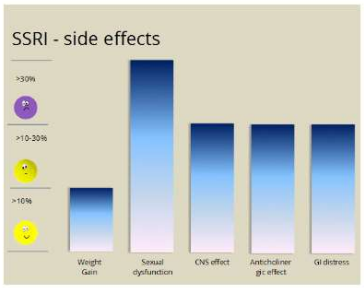
- DAT inhibition can be beneficial in patients with fatigue, poor concentration and amotivation but can result in activation
- The sigma(σ)1 binding properties contribute to its anxiolytic and antipsychotic properties
- Dose – 50-200 mg/day
- Inhibits CYP2D6 – can increase levels of TCA's and Risperidone
- Half life-24-72 hours

Sertraline
1st line (RANZCP Guidelines)

Antidepressant class
SSRI

Principal mechanism of action
Selective 5-HT reuptake blockade.

Prescribed for the following features of depression:
Anxiety



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17. TRAZODONE AND 18. NEFAZODONE

Need to know:

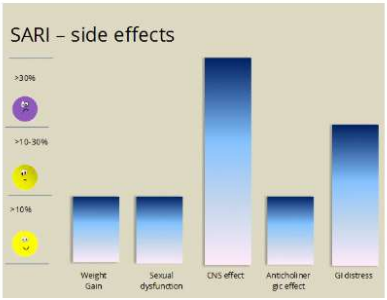
- Nefazodone is not used due to rare liver toxicity
- Trazodone at lower doses (25-150 mg) is used as a hypnotic due to its 5HT2A, α1 and H1 antagonism
- Trazodone acts as an antidepressant at higher doses (150-600mg) due to 5HT2A/C antagonism and SERT inhibition
- Trazodone has biphasic elimination, with a redistribution half-life of about one hour and an elimination half-life of 10-12 hours

Trazodone and Nefazodone (Nefazodone is not mentioned in RANZCP Guidelines)
Typical recommendation is as an adjunctive (RANZCP Guidelines)

Antidepressant class
Serotonin antagonist and reuptake inhibitor (SARI)

Principal mechanism of action
Serotonin 2A/2C antagonist and reuptake inhibitor (at high dosage). At low doses blocks 5-HT2A, Alpha-1 & H1 receptors (hypnotic action).

Prescribed for the following features of depression:
Used when patients do not respond well to 1st line.



19. VENLAFAXINE

Need to know:

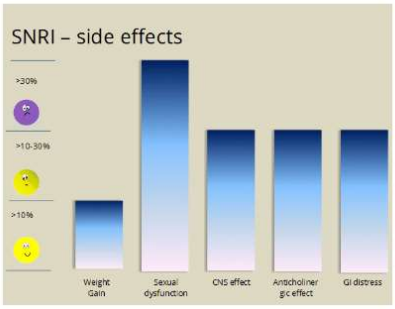
- SERT inhibition at lower doses (75-225 mg)
- NAT inhibition at higher doses (> 225 mg)
- XR version is available to reduce discontinuation symptoms
- Dose 75-375mg /day with food
- Metabolised by CYP2D6/3A4. Due to CYP2D6 genetic polymorphisms there can be significant variability in plasma levels of venlafaxine
- Can increase BP at higher doses
- Headache, sexual dysfunction, sweating and gastrointestinal symptoms are common with venlafaxine. Can also cause withdrawal agitation

Venlafaxine
2nd line (RANZCP Guidelines)

Antidepressant class
SNRI

Principal mechanism of action
Block both serotonergic and nonradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.

Prescribed for the following features of depression:
Treatment Resistant Depression.



20. VILAZODONE

Need to know:

- Serotonin 5HT1A partial agonist (like buspirone) and reuptake inhibitor
- Results in greater serotonin elevation in the brain
- Dose – 10-40 mg/day
- Metabolised by CYP 3A4
- Half-life is 25 hours
- Highly protein bound, therefore, can displace other medications that are protein bound, e.g. warfarin

Vilazodone
Patients who do not respond to SSRI or SNRI antidepressant monotherapy

Antidepressant class
Serotonin partial agonist-reuptake inhibitor (SPARI)

Principal mechanism of action
Inhibition of serotonin (i.e. 5-HT) reuptake and partial agonism of 5-HT1A receptors

Side Effects:
Mild-moderate diarrhoea, nausea and headache. Limited adverse effects on weight and sexual dysfunction.

21.VORTIOXETINE

Need to know:

- Read about vortioxetine in more detail in https://psychscenehub.com/psychinsights/vortioxetine-mechanism-of-action/
- Dose 10-20mg/day
- Long half-life of 66 hours

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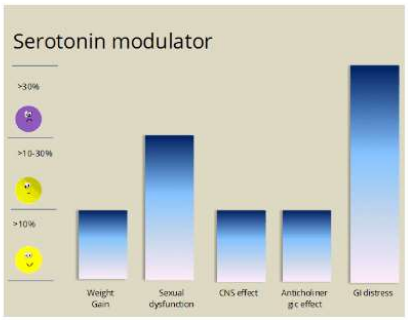
Vortioxetine
2nd line (RANZCP Guidelines)

Antidepressant class
Serotonin Modulator

Principle mechanism of action
5HT1a agonist, 5HT1b partial agonist, 5HT3a and 7 antagonist, 5HT transporter inhibitor.

Prescribed for the following features of depression:
Melancholia, Severe depression, Enhances cognition.



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