GENERALISED ANXIETY DISORDER in ADULTS
PHARMACOLOGICAL TREATMENT PATHWAY 2018[1]

Pan Mersey Area Prescribing Committee

NICE Guidelines: Generalised anxiety disorder and panic disorder[2] in adults (CG 113)[1]

Assessment of Anxiety: a formal diagnosis using the DSM-V classification system[2] is defined by excessive anxiety or worry over more than six months. This is present most of the time in regards to many activities and the patient is unable to manage these symptoms.

- Additionally at least 3 of the following—restlessness, tires easily, problems concentrating, irritability, muscle tension, sleep problems

These symptoms should reduce functioning and should not be due to medications, recreational drugs or other physical health problems.

Be aware that, in primary care, people with GAD often present solely with physical symptoms such as headaches, muscle tension, gastrointestinal symptoms, back pain, and insomnia, and may not readily report worry or psychological distress. [3]

Assessment of suicide risk

Ask directly about suicidal ideation or intent. Risk factors include marked functional impairment and severe co-morbid depressive symptoms.[4] Patients considered at risk or under 30 years old should be seen after one week and frequently until the risk is no longer considered to be significant. All patients should be seen after 2 weeks. All patients should be assessed for drug and alcohol abuse.

Stepped-care model

Step 1: Identification and assessment; education about general anxiety disorder (GAD) and treatment options; active monitoring.
Step 2: Low-intensity psychological interventions: individual non-facilitated self-help, individual guided self-help and psychoeducational groups
Step 3: Choice of a high-intensity psychological intervention (CBT/applied relaxation) or a drug treatment.

FIRST LINE DRUG TREATMENT

Choice of antidepressant
If patient has a previous episode of successful treatment; initiate prior therapy if appropriate, otherwise consider a **generic SSRI** first line (see cost table overleaf) as per NICE recommendations **(note potential for off-label use).**

Paradoxical effect
It should be noted that SSRI and SNRI antidepressants used in anxiety are linked with a paradoxical increase in anxiety, usually during the first 2 weeks of treatment. A low starting dose may reduce the likelihood of this effect. Patients should be counselled to expect this; benzodiazepines can be used in the short term, as stated below.

Monitoring
Under 30 years or suicide risk - review after one week then frequently as appropriate.
Others - review after two weeks then every 2-4 weeks during the first 3 months of treatment and every 3 months thereafter.

Note on benzodiazepines:
As per NICE guidelines; benzodiazepines are not recommended for the treatment of anxiety except for short term use in a crisis (maximum duration 2-4 weeks)

SECOND LINE DRUG TREATMENT – consider referral for mental health specialist opinion

Change drug if unable to tolerate treatment or no response at the maximum tolerated dose within BNF limits[5] after 12 weeks. Check compliance after 2 weeks and confirm diagnosis.

Try an alternative first line SSRI as above e.g. **citalopram, escitalopram sertraline, paroxetine or fluoxetine** or an SNRI e.g. **venlafaxine or duloxetine. Note:** Risk of interactions with citalopram, escitalopram (QTc prolongation[3]); fluoxetine and paroxetine (potent CYP2D6 inhibitors) and fluoxetine (long half-life and prolonged wash-out).

THIRD LINE DRUG TREATMENT and STEP 4:

Complex, treatment-refractory GAD and very marked functional impairment - refer for mental health specialist opinion
If unable to tolerate; or no response after 8/52 (check compliance & diagnosis; exclude/treat common physical problems), and if compliant and no other confounding conditions that cannot be successfully treated, refer to a mental health specialist.

NICE recommends that **pregabalin** may be considered only if SSRIs or SNRIs not tolerated.[6] Due to the flat pricing of this medicine, it should be prescribed **twice daily** with **single capsule** dosing in order to maximise its cost-effectiveness. **Caution**: **Risk of misuse, abuse and dependence with pregabalin.**[4, 7]

Evidence for mirtazapine is limited however it may be useful in patients with co-morbid depression and poor sleep or when SSRIs have caused sexual dysfunction. [6, 8]

At Step 4, patient may require combinations of psychological and drug treatments, combinations of antidepressants, or augmentation of antidepressants with other drugs. **This should only be initiated by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders.**

TREATMENT WORKS

Continue for at least a year after improvement as the likelihood of relapse is high.
If partially responded to drug treatment, consider offering a high-intensity psychological intervention in addition to drug treatment.

DISCONTINUATION

Assume all antidepressants cause withdrawal problems although unlikely with fluoxetine due to long half life.
Ideally reduce dose by 20-25% every 2/52.
Monitor for discontinuation symptoms, reassure if necessary, if severe recommence and reduce more slowly. Particular problems with paroxetine and venlafaxine.

FIRST APC BOARD DATE: 28 May 2014
LAST APC BOARD DATE: 28 Nov 2018

Version: 3
Review date: November 2021
(or earlier if there is significant new evidence relating to this recommendation)

Counselling for Antidepressants used in Anxiety [5,6]

- It may take 2-6 weeks for symptoms to improve
- There may be an initial increase in anxiety, worsening symptoms and suicidal ideation
- Continue taking antidepressants and report any concerns
- Discuss common side effects & interactions
- Advise patients to report intolerable side effects
- Advise that antidepressants are not addictive but withdrawal symptoms can occur on stopping, reducing or missing doses
- Take as prescribed; do not to stop suddenly without advice
- Some antidepressants can impair cognition and can affect ability to drive safely. Do not drive if affected.in this way.
- Avoid alcohol as it can increase risk of side effects
- Don't take St John's wort because of limited evidence and risk of side effects and interactions.

Antidepressant Tolerability Profiles [5]

Fewer sedative effects:	SSRIs
Fewer hypotensive effects:	SSRIs
Fewer cardiac effects:	SSRIs (care citalopram and escitalopram)[3]
Can be stimulating/agitating; may initially worsen anxiety:	SSRIs; Venlafaxine, duloxetine

Relative Safety in Overdose [5]

Lowest risk:	SSRIs (see below), duloxetine
Moderate risk:	venlafaxine, citalopram, escitalopram[3]

Costs per 28 days of *single dose* formulations [7 9] (follow local guidance)

~£1 - £5	Generic SSRIs (some exceptions—see below), mirtazapine, duloxetine, pregabalin, venlafaxine 75 and 150mg Liquids: fluoxetine
~£5 - £10	Fluoxetine 60mg, paroxetine 10mg, venlafaxine 37.5mg Liquids: paroxetine
~£10 - £20	Paroxetine 40mg Liquids: escitalopram, fluoxetine s/f, paroxeti
Above £20	Fluoxetine 10mg, venlafaxine 225mg Liquids: Mirtazapine, pregabalin

Serotonin Syndrome (SS)[6]

Symptoms of serotonin syndrome include (by increasing severity): restlessness, diaphoresis, tremor, shivering, myoclonus, confusion, convulsions, death.

Important Points

Consider side effects, co-morbidities and patient preference.

DO NOT combine antidepressants without specialist mental health recommendation.

Co-morbidity Concerns [5.10]

Cardiac disease:	**Highest Risk** venlafaxine, citalopram, escitalopram[3]
Hepatic impairment:	**Highest Risk** citalopram, escitalopram[3,6]
Renal impairment:	**Highest Risk** citalopram, escitalopram, venlafaxine, pregabalin [6,9]
GI concerns:	Consider prescribing a proton pump inhibitor with an SSRI/SNRI in older adults or those on aspirin/antiplatelet drugs or NSAIDs[1]

Pregnancy and Lactation

When prescribing for patients who are pregnant, breast feeding or planning such contact your local MI service for the latest advice. Alternatively contact your local mental health Medicine Management Team.

Antidepressant Common Interactions [9,10]

5HT drugs & tramadol	Serotonin Syndrome *monitor closely, ideally avoid*
SSRIs & Warfarin	↑ anti-platelet effect, *consider alternative monitor INR*
SSRI&Tamoxifen	*Fluoxetine & paroxetine reduce efficacy*
SSRIs & aspirin	increases anti-platelet effect *consider Rx a gastro protective drug*
SSRIs & NSAIDs	increase GI bleed risk *consider Rx a gastro protective drug*
5HT drugs & St Johns Wort	Serotonin Syndrome **AVOID combination**
SSRIs & Triptans	↑risk of SS with sumatriptan

Hyponatraemia

Hyponatraemia is documented with most antidepressants, with clinical signs including dizziness, lethargy, cramps and seizures. It should be monitored regularly (3 monthly) in those most susceptible (eg. >80yrs, previous history, reduced GFR or associated drugs and comorbidities).

Switching: [5] if more detail required contact your local Mental Health Medicine Management Team

From Drug 1	To Drug 2	Comments
SSRIs, mirtazapine, SNRIs (except venlafaxine), pregabalin	SSRIs, mirtazapine, SNRIs (except venlafaxine), pregabalin	Withdraw Drug 1 then start low dose Drug 2 Wait 4-7days after fluoxetine to low dose Drug 2
SSRIs, mirtazapine, SNRIs (except venlafaxine), pregabalin	venlafaxine	Cross taper cautiously, start venlafaxine at 37.5mg/day, ↑very slowly Fluoxetine—withdraw, start venlafaxine at 37.5mg/day, ↑very slowly

References

1. NICE CG113. Generalised anxiety disorder and panic disorder in adults. January 2011
2. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). Washington, DC.
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5. Bazire S,. 2018. Psychotropic Drug Directory 2018, Lloyd-Reinhold Publications Ltd .
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7. NHS Electronic Drug Tariff, November 2018
8. BAP Guidelines. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder. 2014
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10. SmPCs - various www.medicines.org.uk