

Anxiety Disorders Formulary Guidance [v1.1] (adapted from NICE guideline CG113 and CG159)

1. Introduction

These Guidelines are intended for routine use. However there will be instances where they are not suitable for the patient you are managing, where more bespoke treatment will be necessary. In such instances the rationale for prescribing away from formulary must be recorded.

The advice is split into Generalised Anxiety Disorder (GAD), Social Anxiety Disorder, Panic Disorder, Obsessive Compulsive Disorder and Post Traumatic Disorder (PTSD)

NICE guideline suggest a stepped care* approach for managing of anxiety disorders
(*Adapted from NICE CG113 Anxiety)

- **Step 1:** Identification and assessment; education about anxiety disorder and treatment options, active monitoring.
- **Step 2:** Use of low-intensity psychological interventions: individual non-facilitated self-help, individual guided self help and psycho-educational groups.
- **Step 3:** For inadequate response to step 2 interventions or marked functional impairment. Choice of a high intensity psychological intervention (CBT/applied relaxation) or a drug treatment
- **Step 4:** Complex treatment-refractory anxiety disorder and very marked functional impairment or a high risk of self harm; requiring highly specialist treatment

2. Prescribing in Anxiety States – Key Points

2.1 Pharmacological Treatments

- Pharmacological treatment of anxiety disorders should be considered for severe and persistent symptoms which result in occupational and social disability.
- Psychological interventions should be offered to service users who prefer non-pharmacological treatment or have not benefited from or who are unable to engage with pharmacological interventions.
- The choice of initial treatment should be guided by preference, risks and benefits, side effects, prior treatment history, presence of other physical or psychiatric conditions, suicide risk, potential interaction and cost.
- Discuss the condition and treatment options fully and provide written information.
- Selective Serotonin Reuptake Inhibitors (SSRIs) are effective for a range of anxiety disorders and are suitable first line treatments.
- Inform service users prescribed antidepressants about a delayed onset of effect (at least 2 weeks) likely length of treatment and the need to take medication as prescribed.
- Decisions about off-label use of medications for anxiety disorders should be led by evidence based guidelines and clinical experience. Informed consent for off label use should be gained and documented.

2.2 General Anxiety Disorder (GAD)

- NICE advises that pharmacological interventions are **only** indicated in people with inadequate response to psychological treatments.
- Use low initial doses of antidepressant and titrate up slowly. Initial worsening of anxiety may be evident.
- Antidepressants can take several weeks to have an effect (it usually takes four to six weeks or maximal response to SSRI's), so initial augmentation with a benzodiazepine may be required, the risks of dependence on benzodiazepines should be clearly explained to the

patient.

- For people with GAD, review the effectiveness and side effects of the drug every 2–4 weeks during the first three months of treatment and three monthly thereafter.
- If treatment is effective and tolerable, continue for at least 1 year as the likelihood of relapse is high.

2.3 Social Anxiety Disorder

- Pharmacological treatment is **only** indicated if social anxiety disorder (social phobia) interferes significantly with social or occupational activities.
- SSRIs are considered to be the drugs of choice for the treatment of social anxiety disorder. Standard antidepressant starting doses are indicated for social phobia
- Treatment should be continued for at least 1 year and possibly longer in some cases.
- Co-morbidities e.g. depression, alcohol and substance misuse should be managed.
- Do not offer St John's wort or other over-the-counter medications and preparations for anxiety to treat social anxiety disorder. Explain the potential interactions with other prescribed and over-the-counter medications and the lack of evidence to support their safe use

2.3.1 CAMHS Social Anxiety Disorder

- Do not routinely offer pharmacological interventions to treat social anxiety disorder in children and young people. (NICE CG159)

2.4 Panic Disorder with or without Agoraphobia

- Pharmacologic therapy may be considered if behavioural or cognitive therapy fails.
- Use low initial doses of antidepressant and titrate up slowly, Higher doses may be necessary if standard doses are ineffective.
- There may be an initial exacerbation of anxiety and panic symptoms.
- It can take several weeks before the effects of antidepressants are evident.
- When new medication is started, efficacy and side-effects should be reviewed within 2 weeks of initiation and again at 4, 6 and 12 weeks.
- If there is no improvement after 12 weeks, switch to an alternative antidepressant, if assured compliance has been good.
- Remission of symptoms may take up to 6 months or longer (including 4–6 weeks at the highest comfortably tolerated dose).
- Medication should be continued for 6 months to 1 year after acute response to reduce the risk of recurrence. Long-term treatment may be necessary for some people, and should be available if indicated.
- Antidepressants for panic disorder should be discontinued over at least 4 weeks

2.5 Obsessive Compulsive Disorder

- Offer drug treatment to those with poor response to psychological interventions.
- A combination of pharmacological, behavioural, and psychosocial methods appears to have the most successful long term outcome.
- Doses at the upper end of the indicated dose range may be necessary.
- Most people will not experience substantial improvement until 4-6 weeks after starting medication, and others may show little improvement in the initial 12 weeks.
- If successful, treatment should be continued for 1 – 2 years before considering a gradual withdrawal over 1-2 months, whilst monitoring for any recurrence or relapse. However most will require long term treatment.

2.6 Post-Traumatic Stress Disorder

- Pharmacological treatments should be offered to people who cannot start a psychological therapy or who have gained minimal benefit from it.
- Drug therapy is largely aimed at accompanying symptoms of anxiety or depression NICE recommends the use of paroxetine, mirtazapine, amitriptyline or phenelzine.
- Lower initial dose are recommended although higher target doses (within approved limits)

- may be necessary for full effect.
- Treatment periods of 8- 12 weeks are needed to assess efficacy, if a good response occurs treat for a period of 12 months, before considering a gradual withdrawal.

3. Side-effects and Interactions

- **SSRIs** are better tolerated and safer in overdose than other antidepressants. Common side effects of SSRIs are headache, nausea, and anxiety/agitation, especially when starting treatment usually settle on continued treatment Other side effects are insomnia, tremor, akathisia, sweating, paraesthesias, sexual dysfunction, including diminished libido and difficulty with erection and orgasm, muscle/joint pain, weight gain and manic or psychotic symptoms
- **Tricyclic antidepressants** have similar efficacy to SSRIs but are more likely to be discontinued because of side effects and are toxic in overdose. Common side effects include anxiety, drowsiness, dizziness, agitation, confusion, anticholinergic effects (dry mouth, constipation, urinary retention and blurred vision); cardiovascular effects (hypotension, tachycardia, arrhythmias and other ECG changes - baseline ECG is advised, where appropriate); hepatic changes and changes in blood sugar, weight gain and sexual dysfunction.
- **Monoamine Oxidase Inhibitors (MAOIs)** can have dangerous interactions with some food and drugs, and should be reserved for initiation by consultants. Service users prescribed these drugs should be monitored carefully (blood pressure), and given written dietary advice and information of drug interactions, and what to do in the event of a crisis.
- **Benzodiazepines**, due to risk of dependence, tolerance, withdrawal and rebound symptoms, they should be reserved for short term (2- 4 weeks ideally) at the lowest effective dose, Benzodiazepines can cause sedation, fatigue, ataxia, slurred speech, and risk of falls and fractures. Long term use can cause memory impairments, dependence, impaired alertness and impaired ability to perform skilled tasks, such as driving.
- **Mirtazapine** has few antimuscarinic effects, but causes sedation during initial treatment and is associated with weight gain and rarely blood dyscrasias.
- **Venlafaxine/Duloxetine** Have similar side effects to SSRI's, a cardiac history should be taken before prescribing, paying particular attention to hypertension.
- **Antipsychotics** may be used with caution in anxiety with agitation or psychotic symptoms, when other agents are either ineffective or contraindicated

4. Warnings

(see Depression Formulary Guidance for more detail)

- Antidepressants are associated with an initial worsening of anxiety/agitation and an increased risk of suicidal behaviour and thinking. Monitor closely particularly at the start of treatment, and dosage changes.
- Discontinue antidepressants gradually. Abrupt discontinuation (sometimes reduced or missed doses) of antidepressants can lead to withdrawal symptoms (see depression guidelines)
- Use antidepressants with care in glaucoma, bipolar disorders, prostate hypertrophy, bleeding disorders and seizures.
- Hyponatraemia has been associated with all antidepressants, Mirtazapine may be a suitable choice if this occurs
- SSRIs can increase risk of bleeding. Caution is required in older adults and when used in combination with NSAID's, aspirin or anticoagulants
- SSRIs can increase risk of falls and osteoporotic fractures in people over 50 years.
- Serotonin syndrome can occur with serotonergic drugs and requires emergency management.

5. Further information

1. NICE Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. NICE clinical guideline 113 (2011). www.nice.org.uk/guidance/CG113
2. NICE Obsessive – Compulsive Disorder - NICE: clinical Guideline 31 www.nice.org.uk/CG31
3. NICE. Post Traumatic Stress disorder [WWW.nice.org.uk/CG26](http://www.nice.org.uk/CG26)
4. Evidence- based Guidelines for the pharmacological treatment of anxiety disorders BAP: http://www.bap.org.uk/pdfs/Anxiety_Disorder_Guidelines.pdf
5. BNFOonline www.bnf.org
6. SPC for all the drugs www.medicines.org.uk
7. Psychotropic Drug Directory Bazire 2010

Table 1: GENERALISED ANXIETY DISORDER

1a:

First Line	Relative costs	Notes
Sertraline	£	Not currently licensed for the treatment of GAD; Recommended first-line by NICE If successfully treated previously with another antidepressants, re-initiate prior therapy Offer high-intensity psychological intervention and anxiety management techniques
Second Line	Relative costs	Notes
Alternative SSRI		Offer another SSRI not tried first-line Switch if unable to tolerate treatment or no response after 12 weeks at effective dose - after checking adherence and confirming diagnosis; if partial response consider dose increase.
Paroxetine (liquid)	£ (£££)	Use lower initial doses; high likelihood of discontinuation reactions
Citalopram (liquid)	£ (££)	Off-label use; consider preference, side effects - including QT effects and previous response
Fluoxetine or SNRI	£	Off-label use; consider long half life, preference, side effects and previous response More toxic in overdose than SSRIs; High risk of discontinuation reactions
Venlafaxine (XL)	£ (££)	More toxic in overdose than SSRIs; High risk of discontinuation reactions
Third Line	Relative costs	Notes – SECONDARY CARE INITIATION ONLY
Escitalopram	£££	Branded product and costs are greater than those for generic SSRI
Duloxetine	£££	Branded product and costs are greater than those for generic SSRI/SNRI; Monitor blood pressure
Pregabalin	££££	Branded product and costs are greater than those for generic SSRI; NICE recommends pregabalin only if SSRIs or SNRIs not tolerated; somnolence and dizziness are common
Other Agents	Relative Cost	Notes
Benzodiazepines Diazepam/Lorazepam liquids)	£ (££)	Not routinely recommended except as a short-term measure during crisis because of risk of side effects, dependence and misuse. Useful adjuncts in agitated service users.
Buspirone	££	For short-term use only – delayed onset of action; greater risk of discontinuation due to side effects; Efficacy is reduced in previous extensive use of benzodiazepines; may be useful where benzodiazepines not used before
Propranolol (liquid)	£ (££)	May be useful for somatic symptoms particularly tachycardia; check contraindications
Hydroxyzine	£	Limited effectiveness; use for sedative effect inappropriate

1b: TREATMENT REFRACTORY GENERALISED ANXIETY DISORDER
Initiated and stabilised in Secondary Care

	Relative costs	Notes - Discuss benefits and side effects and consider previous response
General principles		Review current and past treatments and adherence Increase the dose of the current treatment to the maximum dose; Switch to an alternative evidence-based treatment not previously tried Use a combination of psychological interventions and drug treatments.
Antidepressant combinations	£-£££	Seek consultant advice. Limited evidence and side effects and interactions more likely
Antidepressant + Antipsychotic	£-£££	Consultant initiation only. Do not use routinely due to limited evidence of effect; Side effects and interactions more likely. Long-term use of antipsychotic should be avoided.
Antidepressants + other agents, e.g. buspirone, diazepam, pregabalin etc	£-£££	Seek consultant advice. No clear evidence of benefit. Check for contraindications

Table 2: PANIC DISORDER

First Line	Relative costs	Notes
SSRI eg Sertraline Citalopram Paroxetine	£ £ £	Offer psychological therapies and encourage self help Consider preference, previous response, side effects and potential interactions Start with low doses then gradually increase to a full dose, as tolerated Citalopram is more cardiotoxic than other SSRIs and can cause QT prolongation at higher doses Paroxetine has a short half life and a high risk of withdrawal symptoms Fluoxetine and fluvoxamine are not licenced for panic disorder; may be tried if previous good response shown. Consider long half life when switching or stopping fluoxetine. GI side effects are common with fluvoxamine; bradycardia and ECG changes have been noted
Second Line	Relative costs	Notes
Mirtazapine	£	Not licenced for panic disorder but has shown some benefit; sedating; risk of weight gain
Venlafaxine	£-££	Monitor blood pressure; cardiotoxic in overdose
Escitalopram	££	Branded product and costs greater than generic SSRIs; Consider for those who have failed to respond to initial treatments with generic SSRI; Cause dose-dependent QT prolongation
Benzodiazepines	£	Benzodiazepines should not be prescribed except for short term use in severe, distressing and disabling panic symptoms

Table 3: SOCIAL ANXIETY DISORDER

First Line:	Relative Cost	Notes
SSRI e.g. Paroxetine Sertraline Fluoxetine	£ £ £	Offer psychological interventions - CBT is known to be efficacious for long-term treatment SSRIs considered to be the drugs of choice for the treatment of social anxiety disorder Consider combining SSRI + CBT in those with high risk of relapse
Second Line:	Relative Cost	Notes
Alternative SSRI		Offer another SSRI not tried first-line
Fluvoxamine	£	Risk of nausea and vomiting higher with fluvoxamine than other SSRIs; Risk of interactions
Escitalopram	££	Usually 2-4 weeks are necessary to obtain symptom relief with escitalopram
SNRIs		
Venlafaxine	£ - ££	Monitor blood pressure; High risk of discontinuation reactions; cardiotoxic in overdose

Table 4: OBSESSIVE COMPULSIVE DISORDER (OCD)

4a:

First Line:	Relative Cost	Notes
SSRI's		If CBT is not accessible or available, offer drug treatment
Citalopram	£	Also offer CBT if medication not preferred and service users able to engage with CBT
Fluoxetine	£	Paroxetine can cause more weight gain and anticholinergic side effects than are other SSRIs and
Paroxetine	£	greater risk of withdrawal symptoms. Fluoxetine has a long half life. Citalopram causes dose dependant QT interval
Sertraline	£	prolongation.
Second Line:	Relative Cost	Notes
Alternative SSRI	£ - £££	Offer SSRI not tried first line (escitalopram costs greater than for generic SSRIs)
Clomipramine	£	Consider clomipramine when SSRI ineffective or poorly tolerated or when it is the preferred option or where previous good response has been shown. Clomipramine is more likely to induce anticholinergic effects and can cause hypotension and postural dizziness. It can increase levels of liver transaminases and has a potential for seizures and cardiac arrhythmias, particularly at higher doses Consider ECG and blood pressure monitoring in cardiovascular disease
Imipramine	£	Recommended as an option by the British Association of Psychopharmacology but not by NICE

4b: TREATMENT RESISTANT OBSESSIVE COMPULSIVE DISORDER

Third Line:	Relative Cost	Notes – Secondary care initiation and stabilisation
MAOIs		Consider MAOIs in severe OCD where all first-line treatments and most second-line treatments have failed.
Phenelzine	£	
Combinations e.g.		Consultant initiation only Monitor carefully – risk of additive side effects and toxicity;
SSRI + clomipramine	£-££	Off-label use- mirtazapine can also be considered
SSRI + mirtazapine	£-££	
Augmentation e.g.		Antipsychotics (risperidone, quetiapine, haloperidol) can be considered as augmentation strategy
SSRI + antipsychotic	£-£££	where response to SSRI treatment is poor or incomplete
SSRI + trazodone	£-££	May be helpful in alleviating OCD and anxiety as well as sleep disturbances
Benzodiazepines e.g.		Benzodiazepines are not routinely recommended due to limited evidence for efficacy. Only
clonazepam; diazepam	£	consider for short periods for severe anxiety

Table 5: POST TRAUMATIC STRESS DISORDER

First Line:	Relative Cost	Notes
SSRI e.g. Paroxetine Sertraline	£ £	Offer trauma-focused psychological therapies before drug treatment; Continue drug treatment for 12 months if response is evident at 12 weeks Paroxetine and sertraline have current licences for PTSD
Mirtazapine	£	Off-label use; sedation and weight gain likely; blood dyscrasias - monitor
Second Line:	Relative Cost	Notes
Alternative SSRI Citalopram Fluoxetine	£ £	If first line SSRI unsuccessful or not tolerated, a suitable alternative SSRI e.g. citalopram or fluoxetine (off-label use), can be tried
Venlafaxine	£-££	Venlafaxine may be considered as an alternative to SSRIs following non-response - preferred over tricyclics or MAOIs as less adverse effects
MAOIs i.e. phenelzine	£	Consultant only; Can reduce traumatic recollections and nightmares, and repress flashbacks; MAOI treatment requires careful BP monitoring and advice on drug and food interactions
Other Treatments	Relative Cost	Notes
Hypnotics liquids	£ £££	May be appropriate for short-term use only where lack of sleep is a major problem; risk of dependence
Benzodiazepines	£	May be helpful for short-term management of severe anxiety; risk of dependence and misuse
Antiepileptics	£-£££	Carbamazepine, valproate, topiramate – limited benefits in some benefits; off-label for specific symptom clusters; e.g. hyper-reactivity, violent behaviour, angry outbursts, avoidance (social withdrawal) and intrusion