

# **Anxiety Medication Pathway**





# **Prescribing Considerations**

## **Patient Specific Factors**

- Suicide Risk
  - Use of antidepressants (primarily for depression) is associated with reduction in suicide risk at epidemiological level; however studies have found increased suicidal ideation following antidepressant use, particularly in children and young adults
  - Discuss suicidal ideation and possible increased thoughts when offering antidepressants
  - If considered high risk of suicide, limit quantities of medication. See Toxicity section
  - Signpost to support services e.g. <u>Samaritans</u>, <u>Papyrus</u>, <u>Rethink</u>, <u>Staying Safe</u>, <u>The CALM zone</u>, <u>Young Minds</u>, and <u>Recovery College</u>
- Seizure Risk
  - SSRIs are considered low risk, with citalopram/escitalopram as first line followed by Sertraline. Mirtazapine and Duloxetine are also low risk
  - $\circ~$  TCAs should be avoided
- Liver and Kidney Impairment
  - Many medications can accumulate due to reduced metabolism and elimination
  - Doses may need reducing and titrating slower than usual.
  - Avoid medications with anticholinergic or QTc prolonging effects due to urinary retention and electrolyte abnormalities
- Cardiac Disease
  - Sertraline, Fluoxetine and Mirtazapine appear safe
  - See <u>Management of QTc Prolongation</u>

# Key prescribing guidelines

- At all steps, consider non-pharmacological options instead of or in support of drug treatment, e.g. talking therapies
- Request a full list of medical problems and medication from the GP
- Consider causative underlying physical health problems, e.g. hyperthyroidism
- Consider monotherapy within Licensed dose range first (if tolerated)
- Initiation should start low and slowly titrate to reduce the risk of provoked anxiety
- Medication trials should be at least 12 weeks at the maximum tolerable dose due to slow onset of efficacy
- Antidepressants used for alternative indications at low doses should be taken into consideration but are not considered combination treatment
- NMPs must only prescribe within their scope of practice

## Toxicity

- There are significant differences in <u>toxicity</u> between medication classes requiring careful consideration with people with history of overdose
- TCAs have high fatality risk, except for Lofepramine
- SNRIs and most antipsychotics are slightly more toxic in overdose than SSRIs and Mirtazapine which are relatively safe options
- Propranolol is associated with serious risk of toxicity in overdose and is widely under-recognised. Beta-blockers should <u>not</u> be used as alternatives to benzodiazepines. See: Propranolol in the treatment of anxiety in patients at risk of self-harm: <u>Full Guide & Overview Poster</u>

Title	Anxiety Medication Pathway			
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25	Click for front p
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28	ener for norm p

# Licensed Indications

Some SSRIs e.g. Paroxetine and Fluvoxamine are not recommended due to potential for withdrawal effects and interactions via CYP enzyme inhibition, respectively.

### Licensing and Off-label Medicines

- Medications for licensed indications are preferred over offlabel use unless these are recommended by NICE.
- Many off-label uses are supported by a sufficient evidence base and have been approved for routine use by TEWV.
- See: <u>Guidance on Unlicensed and Off-Label Use of</u> <u>Medicines</u> & <u>Safe Transfer of Prescribing Guidance</u> for further information.

	Anxiety Disorders	Generalised Anxiety Disorder	Obsessive Compulsive Disorder	Panic Disorder	Post-Traumatic Stress Disorder	Social Anxiety
ANTIDEPRESSANTS						
SSRIs						
Citalopram	TEWV Off-Label		TEWV Off-Label	Licensed		
Escitalopram		Licensed	Licensed	Licensed		Licensed
Fluoxetine			Licensed			
Sertraline	TEWV Off-Label		Licensed	Licensed	Licensed	Licensed
SNRIs						
Duloxetine	TEWV Off-Label	Licensed				
Venlafaxine	TEWV Off-Label	Licensed*		Licensed*		Licensed*
Other Antidepressants						
Mirtazapine	TEWV Off-Label					
Clomipramine	TEWV Off-Label		Licensed			
MAIOs						
Moclobemide	TEWV Off-Label					Licensed**
Phenelzine	TEWV Off-Label					

\* MR formulation \*\* Manerix brand

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28



# Licensed Indications

Other beta-blockers are also off-label but have not been approved for use. A single patient application process is required for off-label uses that are not pre-approved.

### Licencing and Off-label Medicines

- Medications for licensed indications are preferred over offlabel use unless these are recommended by NICE.
- Many off-label uses are supported by a sufficient evidence base and have been approved for routine use by TEWV.
- See: <u>Guidance on Unlicensed and Off-Label Use of</u> <u>Medicines</u> & <u>Safe Transfer of Prescribing Guidance</u> for further information.

	Anxiety Disorders	Generalised Anxiety Disorder	Obsessive Compulsive Disorder	Panic Disorder	Post-Traumatic Stress Disorder	Social Anxiety
BENZODIAZEPINES	Licensed					
ANTIPSYCHOTICS						
Aripiprazole	TEWV Off-Label					
Risperidone	TEWV Off-Label					
Olanzapine	TEWV Off-Label					
Quetiapine	TEWV Off-Label		TEWV Off-Label			
Other Anxiolytics						
Buspirone	Licensed***					
Doxazosin / Prazosin					TEWV Off-Label	
Lamotrigine			TEWV Off-Label			
Ondansetron			TEWV Off-Label			
Pregabalin		Licensed				TEWV Off-Label
Propranolol	TEWV Off-Label					

\*\*\* Variance in max dose between manufacturers (45-60mg/day)

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# Psychological Intervention

### **First Line Management**

Psychological treatment for all anxiety disorders are considered first line by NICE and many review guidelines, following a stepped care approach:

Focus of the intervention	Nature of the intervention	confidential and effective support available that can
<b>STEP 4:</b> Complex treatment-refractory	Highly specialist treatment, such as complex drug and/or psychological	help you feel better sooner.
impairment, such as self-neglect or a high risk of self-harm	treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care	Talking therapies in County Durham and Darlington NHS Durham and Darlington Talking Therapie
<b>STEP 3:</b> Conditions with an inadequate response to step 2 interventions or marked functional impairment	Choice of a high-intensity psychological intervention (cognitive behavioural therapy [CBT]/applied relaxation) or a drug treatment	Talking therapies in North Yorkshire           NHS North Yorkshire Talking Therapies
<b>STEP 2:</b> Diagnosed conditions not improved after education and active monitoring in primary care	Low-intensity psychological interventions: individual non-facilitated self-help, individual guided self-help, exposure and response prevention [ERP] and psychoeducational groups	Talking therapies in York and Selby NHS York and Selby Talking TherapiesTalking therapies in Teesside Impact on Teesside
<b>STEP 1:</b> All known and suspected presentations of anxiety	Identification and assessment; education about anxiety and treatment options; active monitoring	Title         Anxiety Medication Pathway           Approved by         Drug & Therapeutics Committee         Date of Approval         2           Protocol Number         PHARM-0052-v4.0         Date of Review         1           Click for front page         Click for front page         Click for front page

Self-refer for **NHS talking** therapies

There's a range of

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ed by	Drug & Therapeutics Committee	Date of Approval	27/03/2
ol Number	PHARM-0052-v4.0	Date of Review	01/04/2

2

# Assessment & Rating Scales

#### Assessment

Useful questions to screen for various anxiety states:

### GAD

- During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?
- Are you frequently tense, irritable, and having trouble sleeping?

### OCD

#### Obsessions:

- Are you bothered by repeated and unwanted thoughts of any of the following types:
- Thoughts of hurting someone else
- o Sexual thoughts
- o Excessive concern about contamination/germs/disease
- o Preoccupation with doubts ("what if" questions) or an inability to make decisions
- o Mental rituals (e.g., counting, praying, repeating)
- $\circ$   $\;$  Other unwanted intrusive thoughts
- If you answered "YES" to any of the above: Do you have trouble resisting these thoughts, images, or impulses when they come into your mind?

#### Compulsions:

- Do you feel driven to perform certain actions or habits over and over again, or in a certain way, or until it feels just right? Such as:
- o Washing, cleaning
- Checking (e.g., doors, locks, appliances)
- $\circ$  Ordering/arranging
- Repeating (e.g., counting, touching, praying)
- $\circ \ \ \text{Hoarding/collecting/saving}$
- If you answered "YES" to any of the above... Do you have trouble resisting the urge to do these things?

#### GAD

- GAD-7 Quick and freely available screening and severity assessment tool
- Hamilton Anxiety Rating Scale (HAM-A)
   Clinician rated used widely in literature
- Beck Anxiety Indes (BAI) 21-item selfreported symptom scale

### OCD

- Yale-Brown Obsessive Compulsive Scale (Y-BOCS) – Clinician rated widely used in literature.
- Florida Obsessive-Compulsive Inventory – 20-item self-reported symptom checklist

Page 2 – Panic, PTSD, Social anxiety

#### RCPsych list of rating scales

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

Click for front page

Katzman et al. BMC Psychiatry 2014, 14(Suppl 1):S1

# Assessment & Rating Scales

#### Assessment

Useful questions to screen for various anxiety states:

#### Panic disorder

- Do you have sudden episodes/spells/attacks of intense fear or discomfort that are unexpected or out of the blue? If you answered "YES" then continue
- · Have you had more than one of these attacks?
- · Does the worst part of these attacks usually peak within several minutes?
- Have you ever had one of these attacks and spent the next month or more living in fear of having another attack or worrying about the consequences of the attack?

#### PTSD

• Have you experienced or seen a life-threatening or traumatic event such as a rape, accident, someone badly hurt or killed, assault, natural or man-made disaster, war, or torture?

If you answered "YES" then continue

• Do you re-experience the event in disturbing (upsetting) ways such as dreams, intrusive memories, flashbacks, or physical reactions to situations that remind you of the event?

#### Social anxiety

- Does fear of embarrassment cause you to avoid doing things or speaking to people?
- Do you avoid activities in which you are the centre of attention?
- Is being embarrassed or looking stupid among your worst fears?

Katzman et al. BMC Psychiatry 2014, 14(Suppl 1):S1

### Panic disorder

Panic Disorder Severity Scale (PDSS)
 – 7-item self-reported assessment

#### PTSD

- PTSD Checklist for DSM-5 (PCL-5) Clinician rated widely used in literature
- International Trauma Questionnaire (ITQ) – self-reported tool for ICD-11 PTSD and complex PTSD (CPTSD)

#### Social anxiety

- Liebowitz Social Anxiety Scale (LSAS)
  - 24-item self-reported assessment covering fear and avoidance in different situations

RCPsych list of rating scales

Title	Anxiety Medication Pathway			
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25	
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28	

# Prescribing in Older Adults

## **Age Related Factors**

There are many age-related changes that affect medication absorption, distribution, metabolism and elimination. These include:

- Reduced muscle mass
- Reduced hepatic mass
- Reduced renal function
- Reduced gastrointestinal motility
- Reduced total body water
- Increased total body fat
- Increased blood-brain barrier permeability

In addition, response and tolerability of medication can change over time, which all influences prescribing decisions.

Some medications have dose limits (e.g. Citalopram/Escitalopram) >65yrs.

## Toxicity

- Older age is associated with higher rates of accidental and intentional overdose
- There are significant differences in toxicity between medication classes requiring careful consideration with people with history of overdose
- TCAs have high fatality risk, except for Lofepramine
- SNRIs and most antipsychotics are slightly more toxic in overdose than SSRIs and Mirtazapine which are relatively safe options
- Propranolol is associated with serious risk of <u>toxicity</u> in overdose and is widely under-recognised. Beta-blockers should <u>not</u> be used as alternatives to benzodiazepines. See: Propranolol in the treatment of anxiety in patients at risk of self-harm: <u>Full Guide & Overview Poster</u>

## **Key Prescribing Principles**

- At all steps, consider non-pharmacological options instead of or in support of drug treatment, e.g. talking therapies
- Consider co-morbid physical health problems
- Avoid medications with adrenergic or cholinergic antagonism due to hypotensive and negative cognitive effects (see <u>Medichec</u> for review of adverse effects)
- Caution with medications with long half-lives or active metabolites due to prolonged effects
- Aim for once daily formulations to reduce tablet burden
- Use lower initial doses and consider slower titration than for younger adult population
- Medication trials should be at least 12 weeks at the maximum tolerable dose due to slow onset of efficacy

## Polypharmacy

The diagnosis of multiple medical conditions increases with age and frequently leads to polypharmacy. Medications prescribed for one condition may have negative effects on another or may interact with another medication. Polypharmacy increases the risk of adverse effects and admission to acute hospital. Polypharmacy also increases the risk of poor medication adherence (tablet burden) and administration errors due to confusing medication regimens.

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# **Adjunctive Medicines**

**GREEN**: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

#### Adjunct Medicines

May be used for target symptoms at any stage

- Benzodiazepines (Max 2 weeks)
  - Lorazepam short acting (higher potential for withdrawal / dependence)
  - Diazepam longer acting, can be used once a day Note: Chlordiazepoxide, Clonazepam, and Oxazepam are not supported by TEWV for anxiety
- Promethazine
- Trazodone (up to 150mg/day) at night or in divided doses Potential for serotonin syndrome
- Propranolol for somatic symptoms only Toxic in overdose

#### References

Click for front page

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Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

#### **Role in Treatment**

Adjunct medicines can be used in addition to a regular primary anxiety treatment. These are usually used at low dose or on an as required basis. There is a clear role for benzodiazepines short term to manage initial anxiety symptoms or provoked anxiety that can occur when starting antidepressants. Additional caution is needed with prior history of dependence or substance use. Promethazine can be helpful for sedation but can prolong QT interval. See <u>PSS3</u>: <u>Promethazine for managing agitation and insomnia</u>. Low dose Trazodone may be helpful for sedative qualities either during the day or at night. Propranolol is Licensed for use in physical somatic symptoms of anxiety; however this is not supported by NICE. Propranolol (and other beta-blockers) are associated with serious risk of toxicity in overdose and is widely under-recognised - see Propranolol in the treatment of anxiety in patients at risk of self-harm: <u>Full Guide</u> & <u>Overview Poster</u>. Routine use is discouraged, and appropriate discussion of risks and benefits should be documented.

#### **Evidence Base**

Benzodiazepines are effective short-term for acute anxiety with rapid reduction in symptoms. However, development and tolerance and dependence limit their long-term utility, and courses should be limited to 2 weeks wherever possible. Promethazine is widely use but evidence base is lacking. Trazodone is a 5-HT<sub>2</sub> antagonist/reuptake inhibitor. It is also a potent histamine 1 antagonist which may contribute to its efficacy as a hypnotic. It has a biphasic half-life (first phase 3-6 hours and second phase 5-9 hours). This may be why it helps to promote longer sleep in patients. Its specific action also means that it generally is safe to use with other medications at lower doses for sleep (50-150mg). However, SSRIs, and fluoxetine in particular, can increase plasma levels of trazodone. Higher doses of trazodone in combination with various other antidepressants can increase the risk of serotonin syndrome so if combining for sedative effect then trazodone should be kept to the minimum effective dose.

# GAD <u>Generalised Anxie</u>ty Disorder

**GREEN**: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.





# GAD Generalised Anxiety Disorder

REEN+	Drugs normally recommended or initia
DTV&F)	by a specialist. There may be a further
MBER	formulary and the provision of addition.
∖YY&S)	information may be required for the GF

#### outlined in the provision of additional be required for the GP. **Evidence Base** GAD often follows a chronic course with some patients presenting with active symptoms of the disorder for more than 10 years. Co-morbid depression is found in over 60% of cases and requires simultaneous. Insomnia is common in GAD and

first line treatment should avoid pharmacological options by providing advice on

sleep hygiene and digital CBT apps for insomnia such as Sleepful or Sleepio. High quality randomised control trials (RCTs) support safe and effective use of SSRIs and SNRIs however not all are Licensed for GAD (see Licensed indications). Quetiapine, duloxetine, pregabalin, venlafaxine, and escitalopram have the largest evidence base for efficacy. However, guetiapine is less well tolerated and pregabalin is associated with dependence and a slightly increased risk of congenital malformations in pregnancy. Mirtazapine has evidence of efficacy from small studies based in China. The TCA clomipramine may be useful; however, it has poorer tolerability and potential for serious side effects, particularly in overdose. Buspirone has modest evidence (monotherapy/augmentation), however it has a slow onset of action and efficacy is reduced in recent benzodiazepine use.

Most antidepressants cause a transient increase in anxiety symptoms when treatment is initiated so staring low and slowly titrating is advised.

#### References

#### Associated Guidance

- **Psychotropic Medication Monitoring Guide** ٠
- Management of QTc Prolongation •

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

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#### Click for front page

#### Pregabalin (N)

- Clomipramine (N)
- Quetiapine (monotherapy or augmentation)

Buspirone (monotherapy or

augmentation)

#### PARTIAL RESPONSE

Reassess anxiety using interview

and a validated rating scale

Check effects of medication and adherence

Consider increase to maximum dose for further 6 week trial if tolerated

# Step 5

Step 4

Trial of single/combination drug therapy - 12 weeks

#### Trial of single/combination drug therapy – 12 weeks

Reassess anxiety using interview and a validated rating scale

Check effects of medication and adherence

#### PARTIAL RESPONSE

Consider increase to maximum dose for further 6 week trial if tolerated

# OCD

# **Obsessive-Compulsive Disorder**

**GREEN**: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.



# OCD **Obsessive-Compulsive Disorder**

EEN+	Drugs normally recommended or initiate
V&F)	by a specialist. There may be a further
BER ′Y&S)	formulary and the provision of additional information may be required for the GP.

#### **Evidence Base**

OCD may follow an acute, episodic or chronic course with the majority improving over 10 years from diagnosis. However, remission rates remain low irrespective of treatment, with many experiencing significant long-term symptomatology. Symptoms may respond slowly, and durations of 12 weeks are recommended.

GR

High quality randomised control trials (RCTs) and Cochrane review support safe and effective use of all SSRIs. Comparative studies suggest psychological and pharmacological treatments are equally effective with additional efficacy when combined. The TCA clomipramine has evidence of superior efficacy; however, it has poorer tolerability and potential for serious side effects, particularly in overdose. Combination of Citalopram and Clomipramine is counter-intuitive and increases risk of serotonin syndrome but is based on small randomised open label study is recommended by NICE. ECG monitoring is required and note contraindications listed in the SPC. High dose (150-200% BNF max) SSRIs have been trialled with positive results, though side-effects frequently limit use in practice. Review primary literature if considering use.

In treatment resistant cases there is evidence for augmentation of antidepressants with atypical antipsychotics; risperidone 0.5-3mg (strongest evidence) and aripiprazole 10mg and the antiepileptic lamotrigine, slowly titrated to 100mg daily. 5-HT<sub>3</sub> receptor antagonist ondansetron (4-8mg/day) has a weaker evidence base and may prolong QTc and increases the risk of serotonin syndrome but may limit GI side effects.

Most antidepressants cause a transient increase in anxiety symptoms when treatment is initiated so staring low and slowly titrating is advised.

### Associated Guidance

- **Psychotropic Medication Monitoring Guide** ٠
- Management of QTc Prolongation •

References

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- **Risperidone & SSRI** (augmentation)
- Aripiprazole & SSRI (augmentation)
- Clomipramine & Citalopram (combination) (N) See ECG guidance

Reassess anxiety using interview and a validated rating scale

Check effects of medication and adherence

#### PARTIAL RESPONSE

Consider increase to maximum dose for further 6 week trial if tolerated

# Step 5

Step 4

Trial of single/combination drug therapy – 12 weeks

Trial of single/combination drug therapy – 12 weeks

Lamotrigine & SSRI (augmentation)

- Ondansetron & SSRI (augmentation)
- Above BNF range SSRI

Reassess anxiety using interview and a validated rating scale

Check effects of medication and adherence

#### PARTIAL RESPONSE

Consider increase to maximum dose for further 6 week trial if tolerated

# Panic Disorder

**GREEN**: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

Reassess anxiety using interview

and a validated rating scale

Check effects of medication and adherence

PARTIAL RESPONSE

Consider increase to maximum dose for

further 6 week trial if tolerated

Title Approved by Protocol Numi

Anxiety Medication Pathway Drug & Therapeutics Comm PHARM-0052-v4.0

Click for front page

Date of Approval Date of Review

Step 3

Step 4



# Panic Disorder

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Drugs normally recommended or initiated by a specialist. There may be a further restriction for use outlined in the formulary and the provision of additional information may be required for the GP.

### Step 4 Trial of single/combination drug therapy - 12 weeks Reassess anxiety using interview and a validated rating scale Check effects of medication and adherence Mirtazapine Moclobemide Duloxetine PARTIAL RESPONSE Consider increase to maximum dose for further 6 week trial if tolerated Step 5 Trial of single/combination drug therapy - 12 weeks Reassess anxiety using interview and a validated rating scale Check effects of medication and adherence Clomipramine (N) PARTIAL RESPONSE Consider increase to maximum dose for further 6 week trial if tolerated

#### **Evidence Base**

Panic disorder frequently responds to treatment with around up to 50% experiencing remission. However, some patients remain substantially impaired despite undergoing a succession of psychological and pharmacological treatment.

High quality randomised control trials (RCTs) and Cochrane review support safe and effective use of all SSRIs and SNRIs. Venlafaxine, clomipramine, fluoxetine and benzodiazepines show the strongest effect, though direct comparisons reveal little difference between classes. Benzodiazepines demonstrate better tolerability, but long-term use is discouraged due to development of tolerance and dependence, so may have a role as rescue medication. Duloxetine 30-60mg has a weaker evidence base than Venlafaxine but is generally well tolerated. Mirtazapine 15-30mg may be helpful for co-morbid general anxiety symptoms but appears less effective for panic symptoms. Moclobemide 450mg/day is supported by two trials suggesting efficacy but requires additional care due to interactions and caution with dietary tyramine. Low quality, short-term comparative studies suggest psychological and pharmacological treatments are equally effective with additional efficacy when combined. In more severe cases, pharmacological treatment may be more effective.

Most antidepressants cause a transient increase in anxiety symptoms when treatment is initiated so staring low and slowly titrating is advised.

Reviews for antipsychotic or antiepileptic augmentation highlight poor quality evidence of limited benefits meaning these should only be used resistant cases after exhausting treatments with superior evidence.

	Title Approved by Protocol Number	Anxiety Medication Pathway Drug & Therapeutics Committee PHARM-0052-v4.0	Date of Approval Date of Review	27/03/25 01/04/28
Associated Guidance <ul> <li>Psychotropic Medication Monitoring Guide</li> </ul>		Refer	ences	
Management of QTc Prolongation		Click for fron	t page	

# PTSD

# **Post-Traumatic Stress Disorder**

**GREEN**: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

Reassess anxiety using interview

and a validated rating scale

Check effects of medication and adherence

PARTIAL RESPONSE

Consider increase to maximum dose for

further 6 week trial if tolerated

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Date of Approval

Click for front page

Step 3

Step 4



# PTSD **Post-Traumatic Stress Disorder**

EEN+	Drugs normally recommended or initiate
₩&F)	by a specialist. There may be a further
BER ′Y&S)	formulary and the provision of additional information may be required for the GP.

#### Step 4 Trial of single/combination drug therapy - 12 weeks Reassess anxiety using interview and a validated rating scale Duloxetine Check effects of medication and adherence Mirtazapine Doxazosin / Prazosin (for nightmares) PARTIAL RESPONSE Consider increase to maximum dose for further 6 week trial if tolerated Step 5 Trial of single/combination drug therapy – 12 weeks Reassess anxiety using interview and a validated rating scale Olanzapine Check effects of medication and adherence (augmentation) (N) Risperidone (augmentation) (N) PARTIAL RESPONSE Quetiapine (augmentation) (N) Consider increase to maximum dose for further 6 week trial if tolerated

#### **Evidence Base**

PTSD and complex PTSD should be primarily managed with psychological therapies including trauma-informed CBT and EMDR. Symptoms may be slow to respond however most patients will experience at least a 50% reduction in symptoms after 12 weeks and around 70% reduction by 6 months.

GR

NICE and Cochrane reviews are supportive of SSRIs for those with a preference for medication, with little data to differentiate based on efficacy. Evidence is generally lowmoderate quality with some variation in appraisal statements between organisations. SNRIs and Mirtazapine 15-45mg may also be helpful, but the evidence base is smaller than SSRIs.

Antipsychotics may be helpful for significant functional impairment if other treatments have failed to enable engagement with psychological treatments. Average doses used in trials are lower than other conditions e.g. Olanzapine <10mg, Risperidone <4mg, and Quetiapine <250mg daily. Meta-analysis of RCTs and observational studies suggest benzodiazepines are ineffective for PTSD and the amnestic effects may be counter-productive for processing traumatic experiences. Given the additional issues of tolerance and dependence, benzodiazepine use in PTSD should be minimised.

Doxazosin 4-16mg/day and Prazosin 1-6mg/day have considerable evidence off-label in helping sleep and nightmares associated with PTSD (most literature relates to Prazosin). Both are associated with hypotension, syncope and tachycardia as potential side-effects. Dosing should start low e.g. 1mg at night and titrate weekly (minimum 3 days) with weekly BP monitoring. Trazodone (<150mg) can also be a helpful augmentation for reducing nocturnal symptoms but may increase the risk of serotonin syndrome.

Most antidepressants cause a transient increase in anxiety symptoms when treatment is initiated so staring low and slowly titrating is advised.

### Associated Guidance

- **Psychotropic Medication Monitoring Guide** ٠
- Management of QTc Prolongation •

References

nded or initiated

# **Social Anxiety**

GREEN: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

Reassess anxiety using interview

and a validated rating scale

PARTIAL RESPONSE

Consider increase to maximum dose for

further 6 week trial if tolerated



# **Social Anxiety**

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rugs normally recommended or initiated y a specialist. There may be a further estriction for use outlined in the ormulary and the provision of additional formation may be required for the GP.

### Step 4 Trial of single/combination drug therapy - 12 weeks Reassess anxiety using interview and a validated rating scale Check effects of medication and adherence Moclobemide (N) Pregabalin PARTIAL RESPONSE Consider increase to maximum dose for further 6 week trial if tolerated Step 5 Trial of single/combination drug therapy - 12 weeks Reassess anxiety using interview and a validated rating scale Check effects of medication and adherence Olanzapine (augmentation) Phenelzine (N) PARTIAL RESPONSE Consider increase to maximum dose for further 6 week trial if tolerated

#### **Evidence Base**

The evidence base for managing social anxiety is relatively limited and there is even less for management of treatment resistant cases. Psychological therapies such as CBT can be effective for social anxiety and should be considered first line treatment.

NICE and Cochrane reviews are supportive of SSRIs for those with a preference for medication or when psychological therapies are not sufficiently effective, and they may reduce the risk of relapse. Benzodiazepines can be helpful, but long-term use is discouraged due to development of tolerance and dependence, so may have a role as rescue medication. MAOIs are supported by NICE based on several trials suggesting efficacy but requires additional care due to interactions and dietary restrictions. Phenelzine in doses up to 60mg/day has a larger evidence base than Moclobemide up to 600mg/day. Pregabalin up to 600mg/day is supported by moderate quality evidence for reduction in symptoms, largely if co-morbid generalised anxiety, but the evidence base is smaller than SSRIs.

Reviews for antipsychotic highlight poor guality evidence of limited benefits meaning these should only be used resistant cases after exhausting treatments with superior evidence. Olanzapine up to 20mg in a small number of patients led to minimal improvements and high rates of discontinuation due to adverse effects.

Most antidepressants cause a transient increase in anxiety symptoms when treatment is initiated so staring low and slowly titrating is advised.

#### Associated Guidance

- **Psychotropic Medication Monitoring Guide** ٠
- Management of QTc Prolongation •

References

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Date of Approval

# Switching Medications

To From	Clomipramine	Fluoxetine <sup>1</sup>	MAOIs	Moclobemide	Mirtazapine	Other SSRIs <sup>2</sup>	SNRIs	Trazodone	Vortioxetine <sup>3</sup>
Clomipramine		Withdraw then start fluoxetine at 10mg/day	Withdraw & wait for 3 weeks	Withdraw & wait 1 week	Cross-taper cautiously	Withdraw then start with low dose	Withdraw then start with low dose	Cross-taper cautiously starting with low dose	Withdraw then start with low dose
Fluoxetine	Withdraw & wait for 2 weeks then start low dose		Withdraw & wait 5-6 weeks	Withdraw & wait 5-6 weeks	Cross-taper cautiously	Withdraw & wait 4-7 days then start low dose	Withdraw & wait 4-7 days then start low dose	Cross-taper cautiously	Withdraw & wait 4-7 days then start low dose
MAOIs	Withdraw & wait for 3 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks
Moclobemide	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours		Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours
Mirtazapine	Cross-taper cautiously	Cross-taper cautiously	Withdraw & wait for 2 weeks	Withdraw & wait 1 week		Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Other SSRIs <sup>2</sup>	Withdraw then start with low dose	Withdraw then start fluoxetine at 10mg/day⁴	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously starting with low dose	Cross-taper cautiously starting with low dose <sup>4</sup>
SNRIs	Withdraw then start with low dose	Withdraw then start fluoxetine at 10mg/day <sup>4</sup>	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously	Cross-taper cautiously starting with low dose <sup>4</sup>
Trazodone	Cross-taper cautiously starting with low dose	Cross-taper cautiously	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously		Cross-taper cautiously
Vortioxetine <sup>3</sup>	Withdraw then start with low dose	Cross-taper cautiously starting with low dose <sup>4</sup>	Withdraw & wait 3 weeks	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously starting with low dose <sup>4</sup>	Cross-taper cautiously	
Note: Adapted from The	Maudsley Prescribing Gu	idelines 14th Edition. Advic	e given in this table is part	y derived manufacturers' i	nformation and partly theo	retical. Caution is required	in every instance.	Further Informat	ion

<sup>1</sup> Beware: interactions with fluoxetine may still occur for 5 weeks after stopping fluoxetine because of its long half-life

<sup>2</sup> Includes citalopram, escitalopram, paroxetine and sertraline. Paroxetine initiation not recommended due to the incidence of withdrawal symptoms

<sup>3</sup> Limited data for vortioxetine so extra care required, particularly with fluoxetine and paroxetine which are CYP2D6 inhibitors

<sup>4</sup> Abrupt switch between SSRIs and SNRIs is possible at standard doses e.g. citalopram 20 mg and starting the standard dose of another, e.g. duloxetine 60 mg

SPS Switching Guide

# Deprescribing

#### When to Stop

Anxiety disorders are a major public health problem, and medications are a common and effective treatment strategy. Continuing medication after the resolution of acute symptoms reduces the risk of relapse however the optimum duration of treatment remains uncertain. Discontinuation following up to 1 year of treatment increases the odds of relapse compared with continuing antidepressants. However, most studies used medication taper over 4 weeks which may obscure the true relapse rates through medication withdrawal effects. Current guidelines recommend treatment for at least a year, and some patients may require long-term medication.

De-prescribing should be a collaborative decision following a structured process to reduce the risk of relapse and discontinuation effects. If there are multiple medications prescribed, the order of de-prescribing should be led by clinical need and patient preference e.g. if Mirtazapine and Venlafaxine are prescribed and weight gain is a problem then stopping Mirtazapine would take priority.

#### How to Stop

The flowchart can help guide decisions around discontinuation. Abrupt stopping of anti-depressants and pregabalin can increase the risk of relapse. The faster the discontinuation the greater the risk of relapse and withdrawal symptoms. Linear reductions of dose e.g. Sertraline 150mg, 100mg, 50mg, do not equate to linear reductions of pharmacological effect and tapering plans should be flexible and consider progressive reductions by 25-50% of the previous dose.

All medicines for anxiety have a risk of discontinuation effects ranging from anxiety symptoms to flu-like symptoms and 'electric shock' effects. Discontinuation effects are not harmful but can be very uncomfortable. If discontinuation effects occur a slower taper should be instigated. This is less likely to be required with fluoxetine because of its long half-life. See <u>Withdrawal Risk Assessment Tool</u>.

#### STEP 1: SHOULD I DEPRESCRIBE? – Deprescribing triggers

Risk > benefit, no ongoing benefit, resolution of stressors, alternate coping strategies developed, completion of treatment course, uncertainty about the efficacy for relapse prevention, preference for alternative treatments, adverse effects, tolerability, drug interaction, drug-disease interaction, high drug burden index (DBI), poor adherence

# 1a. Is there a documented indication or symptoms supporting continued use?

#### Inappropriate indication for continued use:

No current anxiety symptoms >6 months

Consult/review with mental health specialist if applicable.

#### Do not deprescribe if:

**Review** 

Recurrent or severe depression or severe OCD or GAD.

If there remains significant risk of relapse, particularly if there are residual anxiety symptoms.

Discuss with mental health specialist if applicable.

#### 1b. Are there adverse effects?

Consider potential adverse effects:

Agitation, anxiety, blurred vision, confusion, constipation, delirium, diarrhoea, dizziness, drowsiness, dry eyes, dry mouth, falls, headaches, hyponatraemia, hypotension, insomnia, myalgia, nausea, palpitations, QT prolongation, rash, rhinitis, sexual dysfunction, sweating, tachycardia, tremor, urinary retention, weakness, weight gain

**1c.** Is this medication likely to cause more harm than benefit? Consider the risks of harm and benefits of continued use.

## **Next Step**

# Deprescribing

#### STEP 2: Does the patient/carer agree with the recommendation to deprescribe?

Over 90% of people would be willing to stop their medicines if recommended by their physician. Following provision of information, discussion and shared decision making, the patient or carer has communicated that they would like to proceed with or decline the deprescribing recommendation. Consider the possible 'nocebo' effect, involving expectations for poor reactions to medication discontinuation.

#### STEP 3: HOW DO I DEPRESCRIBE?

Establish a supportive and trusting relationship with the patient to engage in complex/ sensitive discussions.

Accompany weaning with commencement of relevant non-pharmacological support.

Reduce dose slowly by 25-50% of the daily dose every 2-4 weeks.

In patients prescribed high doses for longer periods a more gradual reduction plan may be more appropriate. Certain antidepressants with a higher risk of discontinuation effects require a more cautious reduction (see withdrawal risk tool).

Consider weaning faster if deprescribing reason due to adverse effects.

Organise prescriber follow up appointment to monitor progress (frequency determined by rate of weaning)

Provide advice on self-monitoring and what to do if symptoms re-occur.

#### 3a) How to wean.

Discuss

Reduce

Initiation: Reduce dose slowly by 25-50% of the daily dose every 2-4 weeks.

#### Adjust according to response.

If no discontinuation effects occur, continue to wean, and stop. Some patients may be able to tolerate faster tapers than others. It is important to work collaboratively and reduce medication at the patient's preferred pace. See Example Deprescribing Plans.

Consider slower weaning (e.g. 12.5%) when reducing to the final lowest dose, as this is where the majority of withdrawal effects present.

Liquid formulations may be required for smaller dose tapering.

Avoid alternate day dosing towards the end, unless using Fluoxetine, as this can cause withdrawal effects. Switching to Fluoxetine can aid with weaning if dosage forms are limited.

#### Adjust according to recurrent symptoms

If recurrent/withdrawal symptoms occur, restart medication at the last effective/tolerable dose.

Recommence weaning after 6-12 weeks with smaller dose reductions (e.g. 5-12.5% of daily dose each month) then stop.

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28



# Deprescribing

#### STEP 4: MONITORING

1-3 Days

Discontinuation symptoms usually occur shortly after dose reductions though can be delayed in if the medication has a long half-life >7 Days Re-emergence of depression or anxiety typically takes longer – weeks or months

### Monitor

Alternative

Management

Common withdrawal symptoms, often called 'discontinuation syndrome' (e.g. anxiety, gastrointestinal effects, insomnia, irritability, and sweating) are usually mild, highly variable and can last up to 6-8 weeks (longer in some cases). See <u>Withdrawal Effects</u>. If severe symptoms (e.g. impaired concentration, motor restlessness, tremor, muscle pain, muscle twitching, tachycardia, hypertension, sweating, generalised tonic-clonic seizures, perceptual disturbance, nausea, bloating, anorexia, severe anxiety, or severe insomnia) occur, restart at the previous lowest effective dose There may be a delay before withdrawal symptoms present for patients on higher doses of fluoxetine because of the longer half-life

#### NON-PHARMACOLOGICAL SUPPORT

Medication is not first-line for many mental health conditions and there are multiple evidence-based non-pharmacological interventions available. See Psychological Support.

Consider:

- Cognitive behavioural therapy
- Guided self-help
- Interpersonal therapy
- Physical activity

- Problem-solving techniques
- Psychodynamic psychotherapy

Withdrawal Effects

- Social prescribing
- Supportive counselling

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

### Withdrawal Risk Tool

Example Deprescribing Plans

# Withdrawal Risk Tool

Duration	Weighting
Short term (1–6 months)	0 points
Intermediate term (6–12 months)	1 point
Long term (1–3 years)	2 points
Very long-term use (> 3 years)	3 points
Antidepressant type	
Lowest risk (Agomelatine)	0 points
Low risk (Vortioxetine,, milnacipran, trimipramine, dosulepin)	1 point
Moderate risk (Citalopram, escitalopram, sertraline, fluoxetine; amitriptyline, nortriptyline, clomipramine, lofepramine	e) 2 points
High risk (Duloxetine, venlafaxine; paroxetine; phenelzine, moclobemide; mirtazapine)	4 points
Dosage	
Minimum therapeutic dosage or lower	0 points
Greater than the minimum therapeutic dosage	1 point
Past experience of withdrawal symptoms	
Stopped antidepressant in past with no withdrawal symptoms/unknown	0 points
Mild to moderate withdrawal symptoms	1 point
Severe withdrawal symptoms	2 points
Very severe withdrawal symptoms	3 points
Low risk = 0 points. Medium risk = $1-4$ points. High risk = $5-8$ points. Very high risk = or >9 points	Return to Deprescribin
itz M.A, et al. Estimating Risk of Antidepressant Withdrawal from a Review of Published Data. CNS Drugs. 2023 Feb;37(2):143-157 itz, M.A, & Taylor, D. M. (2024). The Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs	Click for front page

# Withdrawal Effects

### **Psychological Symptoms**



Images extracted from Horowitz MA, Taylor D. Distinguishing relapse from antidepressant withdrawal: clinical practice and antidepressant discontinuation studies. BJPsych Advances. 2022;28(5):297-311

Most of the listed symptoms are derived from the Discontinuation-Emergent Signs and Symptoms checklist (Rosenbaum 1998).

Symptoms derived from other sources are referenced individually:

Figure 1: Psychological symptoms: a, Fava et al (2015); b, Cosci & Chouinard (2020); c, Valuck et al (2009); d, Rusconi et al (2009). Figure 2: Physical symptoms: a, Cosci & Chouinard (2020).

Title	Anxiety Medication Pathway			
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25	
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28	

**Return to Deprescribing** 

**Physical Symptoms** 

# **Example De-prescribing Plans**

### **Key Deprescribing Principle**

Reductions should be guided by the patient's experience and adjusted to optimise tolerability

### Example Faster De-prescribing Plan

Reduction from e.g. Citalopram 20mg after 6 months treatment

Step 1: Reduce to citalopram 10mg daily for 2 weeks and reassess, Step 2: Reduce to citalopram 5mg daily for 2 weeks and reassess, Step 3: Reduce to citalopram 2.5mg daily for 2 weeks and stop.

Follow up with clinician e.g. fortnightly after discontinuation

#### **Example Slower De-prescribing Plan**

Reduction from e.g. Sertraline 200mg after 12 months treatment

Step 1: Reduce to Sertraline 150mg daily for 4 weeks and reassess, Step 2: Reduce to Sertraline 100mg daily for 4 weeks and reassess, Step 3: Reduce Sertraline 75mg daily for 4 weeks and reassess, Step 4: Reduce Sertraline 50mg daily for 4 weeks and reassess, Step 5: Reduce to Sertraline 25mg daily for 4 weeks and reassess, Step 6: Reduce to Sertraline 12.5mg daily for 4 weeks and stop

Follow up with clinician e.g. fortnightly after discontinuation

### Example Hyperbolic De-prescribing Plan

Further Information

Choice and Medication handy fact sheets for:

Stopping antidepressants
 Specific leaflets for several <u>SSRIs</u>
 Nb. For TEWV employees or patient/carer access only

	Citalopram (mg/day)	Escitalopram (mg/day)	Fluvoxamine (mg/day)	Paroxetine (mg/day)	Sertraline (mg/day)	Duloxetine (mg/day)	Venlafaxine (mg/day)
Step 1	20.0	10.00	50-0	20.0	50.00	60.0	75.0
Step 2	10-0	5-00	30.0	10.0	25.00	30.0	37.5
Step 3	6-0	3.00	20.0	7.0	15.00	15.0	20.0
Step 4	4-0	2.00	15.0	5.0	10.00	10.0	12.0
Step 5	3.0	1.50	10.0	3.0	7.50	6.0	7.0
Step 6	2.0	1.00	5.0	2.0	5.00	4.0	5.0
Step 7	1.0	0.50	2.5	1.0	2.50	2.0	3.0
Step 8	0-5	0.25	0-0	0.5	1.25	1.0	2.0
Step 9	0-0	0.00		0.0	0.00	0.0	1.0
Step 10							0.0

Hyperbolic reductions are calculated based on a desired 10% reduction in serotonin transporter occupancy per step, following the Michaelis–Menten equation:  $Dose = (Occupancy / B_{mm}) \times (ED_{gol} (1-Occupancy / B_{mm}), where B_{mm}$  is the maximal occupancy possible,  $ED_{gol}$  is the dose with 50% occupancy, and both are determined per drug on the basis of PET data (appendix pp 14). Depending on occurrence and tolerability of antidepressant withdrawal symptoms, which might still be occurring when following these steps, the interval between steps (or dosages) can be adjusted via shared decision making by the patient and physician. This Taskforce does not consider prolonged use of any dosage of these discontinuation steps without further attempts of discontinuation as being rational pharmacotherapy. SNRI-servotonin-norepinephrine reuptake inhibitor.

Table: Steps in dosing to discontinue SSRIs and SNRIs in case of one or more risk factors for acute withdrawal syndrome

Extract from Ruhe, H.G., et al. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The lancet. Psychiatry, 6(7), 561–562.

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col Number	PHARM-0052-v4.0	Date of Review	01/04/28		
	Return to Deprescribing				
	Click for front page				

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# **Appendix 1: Reference List**

#### ~ • •

GAD	
Allgulander C., et al. (2001) Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: Twenty-four-week placebo- controlled dose-ranging study. Br J Psychiatry 179(1) 15-22	Askari N., et al. (2012) Granisett Baldwin D.S. et al (2014) Evider
Baldwin D.S., et al. (2011) Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharm 14, 697-710	compulsive disorder: a revision of
Baldwin D.S. et al (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-	Berlin H.A. et al. (2011) Double-
compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology.	716-21
J Psychopharm, 28(5) 403-39	Bloch M.H, et al. (2010) Meta-ar
Bandelow B., et al. (2010) Extended-release quetiapine fumarate (quetiapine XR): A once-daily monotherapy effective in generalized anxiety	Borue X., et al. (2015) Biological
disorder. Data from a randomized, double-blind, placebo- and active-controlled study. Int J Neuropsychopharm 13, 305-320	Disorders 6, 7-26
Bandelow B, et al. The German Guidelines for the treatment of anxiety disorders: first revision. Eur Arch Psychiatry Clin Neurosci. 2022	Bruno A. et al (2012) Lamotrigin
Jun;272(4):571-582.	1456-62
Bech P., et al. (2010) Relapse prevention and residual symptoms: A closer analysis of placebo-controlled continuation studies with	Del Casale, A., et al. (2019). Psy
escitalopram in major depressive disorder, generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder. J Clin	17(8), 710–736.
Psychiatry 71(2) 121-129	Depping, A. M., et al. (2010). Se
Boschen, M.J. (2011) A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. Canadian Journal of	CD008120.
Psychiatry 56(9) 558-66	Dold M. et al (2013) Antipsychot
Chessick C.A., et al. (2009) Azapirones for generalized anxiety disorder (Review). Cochrane Database of Systematic Reviews, Issue 1	meta-analysis of double-blind, ra
Davidson J.R., et al. (2010) A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). J Psychopharmacol 24(1)	Fineberg N.A., et al. (2015) Obse
3-26	Psychiatry Research 227, 114-2
Depping, A. M., et al. (2010). Second-generation antipsychotics for anxiety disorders. The Cochrane database of systematic reviews, (12),	Higuma H. et al. (2012) Aripipraz
CD008120.	Journal of Biological Psychiatry
Endicott J., et al. (2007) Duloxetine treatment for role functioning improvement in generalized anxiety disorder: Three independent studies. J	Katzman MA, et al. (2014) Cana
Clin Psychiatry 68(4) 518-524	compulsive disorders. BMC Psy
Fagan, H. A., Baldwin, D. S. (2023). Pharmacological Treatment of Generalised Anxiety Disorder: Current Practice and Future Directions.	Marazziti D., et al. (2008) Effecti
Expert Review of Neurotinerapeutics, 23(6), 535–548.	Spectr 13(11) 971-6
Gambi F., et al. (2005) Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. J Psychopharma.col 19(5) 483- 487	compulsive disorder and body d
Gelenberg A.J., et al. (2000) Efficacy of venlafaxine extended-release capsules in non-depressed outpatients with generalized anxiety	The Royal College of Psychiatris
disorder: A 6-month randomized controlled trial. JAMA 283(23) 3082-3088	National Institute for Health and
Katzman MA, et al. (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-	NICE clinical guideline 31 'Obse
compulsive disorders. BMC Psychiatry. 14 Suppl 1(Suppl 1):S1.	dysmorphic disorder' (2005). Evi
Maneeton N., et al. (2016) Quetiapine monotherapy in acute treatment of generalized anxiety disorder: a systematic review and meta-	Pallanti S., et al. (2004) Respons
analysis of randomized controlled trials. Drug Des Devel Ther 12(10) 259-76	without comorbid depression: A
National Collaborating Centre for Mental Health. (2011) Generalised anxiety disorder in adults: management in primary, secondary and	Pallanti S., et al. (2014) Ondans
community care. NICE CG 113. Leicester and London (UK): The British Psychological Society and The Royal College of Psychiatrists	serotonin reuptake inhibitors: Im
National Institute for Health and Clinical Excellence. (2012) Generalised anxiety disorder in adults: A summary of selected new evidence	24, 375-80
relevant to NICE clinical guideline 113 'Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management	Pampaioni I., et al. (2010) High-o
In primary, secondary and community care (2011). Evidence Update 22. NICE	Psychopharmacol 24(10) 1439-1
National institute for Health and Clinical Excellence. (2013) Evidence Summary: unlicensed or on-label medicine (ESOOM12): Generalised	Phillips K. (1996) An open study
alized by Ological Automatical Englishing and the Therapy of Application Disorders and Obecesive Computative Disorders	Selteni E. et al. (2010) A double
rightoria, et al. (2010) men race of Antipsycholics in the merapy of Antiety Disorders and Obsessive-Computive Disorders. Diarmagnatharany 35(2) 175-88	Bsychopharmacol 25(6) 500 12
internationary $50(2)$ in 5-00 Baranological treatments for generalised any lety disorder: a systematic review and network meta-analysis. Lancet	Taylor DM Barnes TPE Vo
	rayior, D.ivi., Dames, T.K.E., To
Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021	Title Anxiety
	Approved by Drug 8

#### - - -

ron adjunct to fluvoxamine for moderate to severe obsessive-compulsive disorder. CNS Drugs 26(10) 883-92 nce-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessiveof the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharm, 28(5) 403-39 blind, placebo-controlled trial of topiramate augmentation in treatment-resistant OCD. J Clin Psychiatry 72(5)

nalysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Molec Psych 15, 850–55 I treatments for obsessive-compulsive and related disorders. Journal of Obsessive-Compulsive and Related

e augmentation of SSRIs in treatment-resistant obsessive-compulsive disorder, J Psychopharmacol 26(11)

ychopharmacological Treatment of Obsessive-Compulsive Disorder (OCD). Current neuropharmacology,

cond-generation antipsychotics for anxiety disorders. The Cochrane database of systematic reviews, (12),

tic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder; a andomized, placebo-controlled trials. The International Journal of Neuropsychopharmacology 16, 557-74 essive-compulsive disorder (OCD): Practical strategies for pharmacological and somatic treatment in adults. 25

zole augmentation in 13 patients with refractory obsessive-compulsive disorder: A case series. The World 13(1) 14-21

dian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessivechiatry. 14 Suppl 1(Suppl 1):S1.

iveness of long-term augmentation with citalopram to clomipramine in treatment-resistant OCD patients. CNS

r Mental Health, (2006) Obsessive compulsive disorder: Core interventions in the treatment of obsessive ysmorphic disorder. National Clinical Practice Guideline Number 31. The British Psychological Society and sts

Care Excellence. (2013) Obsessive-compulsive disorder: A summary of selected new evidence relevant to essive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body idence Update 47. NICE

se acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients pilot study. J Clin Psychiatry 65(10) 1394-99

etron augmentation in patients with obsessive-compulsive disorder who are inadequate responders to provement with treatment and worsening following discontinuation. European Neuropsychopharma cology

dose selective serotonin reuptake inhibitors in OCD: a systematic retrospective case notes survey. J 1445

of buspirone augmentation of serotonin-reuptake inhibitors in body dysmorphic disorder. 2(1) 175-80

e-blind, placebo-controlled pilot study of ondansetron for patients with obsessive compulsive disorder. Hum

pung, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# **Appendix 1: Reference List**

#### Panic Disorder

Andrisano C., et al. (2013) Newer antidepressants and panic disorder: a meta-analysis. Int Clin Psychopharmacol 28(1) 33-45 Baldwin D.S. et al (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessivecompulsive disorder: a revision of the 2005 quidelines from the British Association for Psychopharmacology. J Psychopharm, 28(5) 403-39 Bakker, A., et al. (2005), Evidence-based pharmacotherapy of panic disorder. The international journal of neuropsychopharmacology, 8(3), 473-482 Batelaan N.M. et al. (2012) Evidence-based pharmacotherapy of panic disorder an update. International Journal of Neuropsychopharmacology 15, 403-15 Bighelli, I., et al. (2016). Antidepressants and benzodiazepines for panic disorder in adults. The Cochrane database of systematic reviews, 9(9), CD011567. Breilmann, J., et al. (2019). Benzodiazepines versus placebo for panic disorder in adults. The Cochrane database of systematic reviews. 3(3), CD010677. Depping, A. M., et al. (2010). Second-generation antipsychotics for anxiety disorders. The Cochrane database of systematic reviews, (12), CD008120. Furukawa, T. et al. (2007), Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. The Cochrane database of systematic reviews, 2007(1), CD004364. Guaiana G, et al. (2023) Pharmacological treatments in panic disorder in adults: a network meta-analysis. Cochrane Database of Systematic Reviews 2023, Issue 11. Art. No.: CD012729. Imai, H., et al. (2014). Azapirones versus placebo for panic disorder in adults. The Cochrane database of systematic reviews, (9), CD010828. Krüger M.B., et al. (1999) The efficacy and safety of moclobemide compared to clomipramine for panic disorder. Eur Ar Psych Clin Neuro 249 Suppl 1 S19-S24 Lecrubier Y., Judge R. (1997) Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. 95(2) 153-160 Masdrakis, V. G., et al. (2021). Anticonvulsant and antipsychotic medications in the pharmacotherapy of panic disorder: a structured review. Therapeutic advances in psychopharmacology, 11, 20451253211002320. National Institute for Health and Clinical Excellence. (2011) Generalised anxiety disorder and panic disorder in adults: management. CG113 NICE Pande A.C., et al (2000) Placebo controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacology 20(4) 467-71 Pollack M., et al. (2007) A RCT of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology 194(2) 233-42 Ribeiro L., et al. (2001) Mirtazapine versus fluoxetine in the treatment of panic disorder, Braz J Med Biol Res 34(10) 1303-1307 Simon N.M., et al. (2009) Open-label support for duloxetine for the treatment of panic disorder. CNS Neuroscience & Therapeutics 15(1) 19-Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021 Tiller J.W. et al. (1999) Moclobemide and fluoxetine for panic disorder. Eur Arch Psychiatry Clin Neurosci 249 Suppl 1 S7-10 Watanabe, N., et al. (2009). Combined psychotherapy plus benzodiazepines for panic disorder. The Cochrane database of systematic reviews, (1), CD005335,

#### PTSD

Baldwin D.S. et al (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessivecompulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharm, 28(5) 403-39 Berger W., et al. (2008) Pharmacologic Alternatives to Antidepressants in Posttraumatic Stress Disorder: A Systematic Review. Prog Neuropsychopharmacol Biol Psychiatry 33(2): 169-80

Bernardy, N. C., et al. (2015). Psychopharmacological strategies in the management of posttraumatic stress disorder (PTSD): what have we learned?. Current psychiatry reports, 17(4), 564.

Bisson, J. I., et al. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. The Cochrane database of systematic reviews, 2013(12), CD003388.

Burback, L., et al. (2024). Treatment of Posttraumatic Stress Disorder: A State-of-the-art Review. Curr neuropharmacol, 22(4),557–635. Byers M.G., et al. (2010) Prazosin versus quetapine for injettime Posttraumatic Stress Disorder Symptoms in veterans: An assessment of Iong-term comparative effectiveness and safety. J Clin Psychopharmacol 30(3) 225-29

Carey P., et al. (2012) Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. Human Psychopharmacology 27(4) 386-91

De Berardis, D., et al. (2015). Targeting the Noradrenergic System in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis of Prazosin Trials. Current drug targets, 16(10), 1094–1106.

Guina, J., et al. (2015). Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. Journal of psychiatric practice, 21(4), 281–303. Hoskins M., et al. (2015) Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. The British Journal of Psychiatry 206 93-100

Ipser, J. C., et al. (2012). Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). The international journal of neuropsychopharmacology, 15(6), 825–840.

Kung S., et al. (2012) Treatment of nightmares with prazosin: A systematic review. Mayo Clin Proc 87(9) 890-900 National Institute for Health and Care Excellence. (2018) Evidence reviews for pharmacological interventions for the prevention and treatment of PTSD in adults: Post-traumatic stress disorder: Evidence review F. London: NICE; 2018 Dec. (NICE Guideline, No. 116.) National Collaborating Centre for Mental Health. (2005) Post-traumatic stress disorder: The management of PTSD in adults and children in primary and secondary care. National Clinical Practice Guideline Number 26. Leicester and London (UK): Gaskell and the British Psychological Society

National Institute for Health and Clinical Excellence. (2013) Post-traumatic stress disorder: A summary of selected new evidence relevant to NICE clinical guideline 26 'The management of PTSD in adults and children in primary and secondary care' (2005). Evidence Update 49. Raskind, M.A., et al. (2018). Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans. The New England journal of medicine, 78(6), 507–517.

Richards, A., et al. (2018). An Open-Label Study of Doxazosin Extended-Release for PTSD: Findings and Recommendations for Future Research on Doxazosin. Focus (American Psychiatric Publishing), 16(1), 67–73.

Rodgman C., et al. (2016) Doxazosin XL reduces symptoms of posttraumatic stress disorder in veterans with PTSD: a pilot clinical trial. J Clin Psychiatry. 77(5): 561-5

Stein M.B., et al. (2002) Adjunctive olanzapine for SSRI-resistant combat-related PTSD: A double-blind, placebo-controlled study. Am J Psychiatry 159(10) 1777-79

Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021 Taylor H.R., et al. (2008) Prazosin for treatment of nightmares related to posttraumatic stress disorder. Am J Health-Syst Pharm 65 716-22 Walderhaug E., et al. (2010) Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. Pharmacopsych 43(2) 45-9 Williams, T., et al. (2022). Pharmacotherapy for post traumatic stress disorder (PTSD). The Cochrane database of systematic reviews, 3(3), CD002795.

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# **Appendix 1: Reference List**

#### **Social Anxiety**

Arre T.F. (2003) Phenelzine efficacy in refractory social anxiety disorder: A case series. Nord J Psychiatry 57(4) 313-315 Baldwin D.S. et al (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessivecompulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharm, 28(5) 403-39 Bandelow B, et al. The German Guidelines for the treatment of anxiety disorders: first revision. Eur Arch Psychiatry Clin Neurosci. 2022 Jun;272(4):571-582.

Barnett S.D., et al. (2002) Efficacy of olanzapine in social anxiety disorder: a pilot study. J Psychopharmacology 16(4) 365-368 Blanco C., et al. (2010) A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. Arch Gen Psychiativ 67(3) 286-295

Blanco C., et al. (2013) The evidence-based pharmacotherapy social anxiety disorder. Int J Neuropsychopharm 16 235-249

Davidson J. (2003) Pharmacotherapy of social phobia. Acta Psychiatr Scand Suppl 417 65-71

Depping, A. M., et al. (2010). Second-generation antipsychotics for anxiety disorders. The Cochrane database of systematic reviews, (12), CD008120.

Feltner D.E., et al. (2011) Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixeddose study. International Clinical Psychopharmacology 26(4) 213-20

Gelernter, C. S., et al. (1991). Cognitive-behavioral and pharmacological treatments of social phobia. A controlled study. Archives of general psychiatry, 48(10), 938–945.

Heimberg, R. G., et al. (1998). Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. Archives of general psychiatry, 55(12), 1133–1141.

Katzman MA, et al. (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessivecompulsive disorders. BMC Psychiatry. 14 Suppl 1 (Suppl 1):S1.

National Collaborating Centre for Mental Health. (2013) Social anxiety disorder: Recognition, assessment and treatment. National Clinical Practice Guideline Number 159. Leicester and London (UK): Gaskell and the British Psychological Society

Pande A.C., et al. (1999) Treatment of social phobia with gabapentin. J Clin Psychopharmacology 19 341-48

Pande A.C., et al. (2004) Efficacy of the novel anxiolytic pregabalin in social anxiety disorder. J Člin Psychopharmacology 24(2) 141-49

Prasko, J., et al. (2006). Moclobernide and cognitive behavioral therapy in the treatment of social phobia. A six-month controlled study and 24 months follow up. Neuro endocrinology letters, 27(4), 473–481

Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021 Williams, T., et al. (2017). Pharmacotherapy for social anxiety disorder (SAnD). The Cochrane database of systematic reviews, 10(10), CD001206.

#### CAMHS

Baldwin D.S. et al (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessivecompulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharm, 28(5) 403-39 Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021

#### **Adjunct Medicines**

de las Cuevas, et al. (2003). Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology, 167(3), 297–303. Edinoff, A.N., et al. (2021). Benzodiazepines: Uses, Dangers, and Clinical Considerations. Neurology international, 13(4), 594–607. Fagiolini A., et al (2012) Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs 26(12) 1033–1049 Generali J.A., et al (2015) Trazodone: Insomnia (Adults). Hosp Pharm 50(5): 367-369

Hirschtritt, M.E., et al. (2021). Balancing the Risks and Benefits of Benzodiazepines. JAMA, 325(4), 347–348.

Lader M. (2011). Benzodiazepines revisited--will we ever learn?. Addiction (Abingdon, England), 106(12), 2086–2109.

Nutt, D. J., et al. (2001). New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. The British journal of psychiatry : the journal of mental science, 179, 390–396.

Saleu-Zyhlarz G.M., et al (2003) Confirmation of the neurophysiologically predicted therapeutic effects of trazodone on its target symptoms depression, anxiety and insomnia by postmarketing clinical studies with a controlled-release formulation in depressed outpatients. Neuropsychobiology 48(4)194-208

Taylor, D.M., Barnes, T.R.E., Young, A.H. The Maudsley Prescribing Guidelines in Psychiatry, 14th ed., John Wiley & Sons, 2021 Vinkers, C. H., & Olivier, B. (2012). Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABA(A) Receptor Modulators?. Advances in pharmacological sciences, 2012, 416864.

Willems, I. A., et al. (2013). Tolerance to benzodiazepines among long-term users in primary care. Family practice, 30(4), 404–410.
Žourková A., et al (2006) Gender differences in efficacy and sexual function in long-term trazodone treatment. Int J Psych Clin Prac 10(3) 154-59

Title	Anxiety Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	27/03/25
Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# Definitions

## Combination

A combination of two or more treatments, each of which represents an antidepressant alone, i.e. it adds an extra effect without altering the action of the first drug

### Augmentation

Augmentation means adding another drug that by itself is not an antidepressant, but that may improve the efficacy of the original antidepressant.

### **Partial Response**

Failure to respond completely to a course of single drug therapy

## **Off-label**

Prescribing a Licensed medication for a condition outside of their license

### Unlicensed

Prescribing a medicine that does not have a UK marketing license

### СВТ

Cognitive behavioural therapy (CBT) is a type of psychotherapy that helps people change their thoughts and behaviours to improve their feelings

#### EMDR

Eye movement desensitization and reprocessing (EMDR) is a psychological therapy that helps people process traumatic memories and feelings

#### EPR

Exposure and response prevention is a behavioural therapy that helps people with OCD learn to control their obsessions and compulsions

#### NMP

Non-medical prescriber

#### SSRI

Selective serotonin reuptake inhibitor

#### SNRI

Serotonin and noradrenaline reuptake inhibitor

#### TCA

Tricyclic antidepressant

#### MAOI

Monoamine oxidase inhibitor

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Protocol Number	PHARM-0052-v4.0	Date of Review	01/04/28

# Document Changes

Ver.	Date of change	Details of change
4.0	27/3/25	<ul> <li>New format and full refresh</li> <li>Evidence base updated</li> <li>Inclusion of slides on assessment, rating scales, psychological support, and deprescribing</li> <li>Topiramate removed in line with restrictions related to the pregnancy prevention program</li> <li>Gabapentin removed due to lack of evidence and general lack of use</li> <li>Toxicity information strengthened</li> <li>Duration and dosage information amended to promote longer trials at therapeutic doses</li> <li>Promethazine added to adjunct medicines in line with off-label guidance and routine clinical use</li> <li>Fluoxetine added to step 4 for PTSD in line with NICE</li> <li>Mirtazapine added to step 4 for PTSD in line with NICE</li> <li>Buspirone amended to monotherapy or augmentation, unclear rational for SSRI only augmentation</li> <li>Prazosin/Doxazosin reworded to promote Doxazosin due to supply problems</li> </ul>

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