Supplement 2: Switching between SSRI and SNRI medications

The choice of switching strategy is influenced by the following:

- Reason for switch (e.g. unable to tolerate adverse effects, inadequate response)
- Characteristics of the medications involved (e.g. half-lives, risk of discontinuation symptoms, potential for drug-drug interactions, dose and duration of current treatment)
- Patient factors (e.g. sensitivity to adverse effects, risk of relapse, ability to understand and administer medication schedule, experience of previous switches)

Patients should be provided with clear instructions and monitored closely when switching between medications. The following is a brief guide only; specialist advice or management can be sought at any point.

Switching from fluoxetine[53,58,59]

To another SSRI (escitalopram, sertraline, fluvoxamine, paroxetine)	Stop fluoxetine or consider tapering gradually to 20mg (if dose ≥40mg daily) before stopping → Washout for 4–7 days → Then start new SSRI at low dose 
To an SNRI (duloxetine, venlafaxine)	Stop fluoxetine or consider tapering gradually to 20mg (if dose ≥40mg daily) before stopping → Washout for 4–7 days → Then start SNRI at low dose  ⚠ Fluoxetine may increase exposure to duloxetine and venlafaxine as it is a strong CYP2D6 inhibitor.

Additional notes:

- Fluoxetine and its active metabolite have a long elimination half-life (4–16 days). The risk of drug-drug interactions may persist for several weeks after stopping fluoxetine.
- The duration of washout period can be individualised, based on clinical judgment.
- Other approaches (e.g. direct switch or cross-tapering) may be suitable on a case-by-case basis – seek specialist advice, if needed.[60,61]

Switching from other SSRIs (excluding fluoxetine)[53,58,59]

To another SSRI (escitalopram, sertraline, fluvoxamine, paroxetine, fluoxetine)	**Option 1:** Direct switch to the new SSRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of new SSRI 	Under this option, cross-tapering may be suitable. 
To an SNRI (duloxetine, venlafaxine)	**Option 1:** Direct switch to the SNRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of SNRI 	Under this option, cross-tapering cautiously may be suitable for SSRIs that do not interact with SNRIs. 
		⚠ Paroxetine may increase exposure to duloxetine and venlafaxine as a strong CYP2D6 inhibitor. ⚠ Fluvoxamine may increase exposure to duloxetine as a strong CYP1A2 inhibitor.	

Additional notes:

- Option 1: While a similar mechanism of action may lessen discontinuation symptoms, patients who have taken an antidepressant for at least 6 weeks remain at risk of such effects. Alternative approaches that involve tapering can be considered.
- Option 2 is a more conservative strategy with the lowest risk of drug-drug interactions and additive adverse effects.
- Cross-tapering:
  - Entails gradually reducing the first medication while titrating up the new one from low dose, including a period in which both medications are taken.
  - Suitable patients are those able to manage complex medication regimen or have support from competent caregivers.

Switching from SNRIs[53,58,62]

To an SSRI (escitalopram, sertraline, fluvoxamine, paroxetine, fluoxetine)	**Option 1:** Direct switch to the SSRI on the next day (consider usual dose; tailor based on individual factors) 	**Option 2:** Taper then start low dose of SSRI 	Under this option, cross-tapering cautiously may be suitable for SSRIs that do not interact with SNRIs.  ⚠ Paroxetine and fluoxetine (strong CYP2D6 inhibitors) may interact with duloxetine and venlafaxine. ⚠ Fluvoxamine (strong CYP1A2 inhibitor) may interact with duloxetine.
To another SNRI (duloxetine, venlafaxine)	**Option 1:** Direct switch if duloxetine dose <60 mg daily or venlafaxine dose <150 mg daily 	**Option 2:** Taper then start low dose of new SNRI 	Under this option, cross-tapering cautiously may be suitable. 

Additional notes:

- Option 1: While a similar mechanism of action may lessen discontinuation symptoms, patients who have taken an antidepressant for at least 6 weeks remain at risk of such effects. Alternative approaches that involve tapering can be considered.
- Option 2 is a more conservative strategy with the lowest risk of drug-drug interactions and additive adverse effects.
- Cross-tapering:
  - Entails gradually reducing the first medication while titrating up the new one from low dose, including a period in which both medications are taken.
  - Suitable patients are those able to manage complex medication regimen or have support from competent caregivers.

A note on switching from an SSRI or SNRI to other antidepressants (mirtazapine, agomelatine)[53,58,59,61]

- When switching to agomelatine or mirtazapine, the SSRI or SNRI should be tapered gradually (fluoxetine can be stopped, or tapered if dose ≥ 40mg daily). Some discontinuation symptoms may nonetheless be experienced as the mechanism of action is different.
- For SSRIs other than fluvoxamine: Taper then start agomelatine or mirtazapine at low dose; cross-tapering is possible.
- For fluvoxamine: Consider tapering fluvoxamine and stopping for 4–7 days (washout) before starting agomelatine, due to drug-drug interaction.