Treatment of depression in inflammatory bowel disease

Document authors

Siobhan Gee

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Siobhan Gee

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The Quality Centre is how we work with staff, patients, and carers, alongside colleagues at Kings College London and Kings Health Partners, to drive improvement, innovation and value-based commissioning in mental health care. All our work is underpinned by the principles of collaboration, inclusion, shared learning and the use of data intelligence to achieve our vision of optimising health outcomes for the populations we serve, whilst bringing together our learning for wider benefit.

Treatment of depression in inflammatory bowel disease

Contents

1 Introduction

1.1 Scope

This document makes treatment recommendations for adults aged 18 and over, diagnosed with depression, who have a comorbid diagnosis of inflammatory bowel disease (IBD).

This guideline does not cover:

- Diagnosis of depression
- Non-pharmacological treatments
- Treatment-resistant depression
- Non-depressive symptoms (e.g. psychosis)

1.2 Treatment of depression

Depression is characterised by a depressed mood and/or loss of pleasure in most activities[1]. In general, antidepressants are not recommended as a first-line treatment for recent-onset, mild depression[1]. For patients with moderate to severe depression, antidepressants should be prescribed.

NICE recommend choosing a generic selective serotonin reuptake inhibitor (SSRI) first-line. Choice of drug should be based on patient preference, likelihood of side effects, and potential for interactions with concurrent medications or comorbidities. In an absence of any medical considerations, sertraline, fluoxetine, citalopram and escitalopram are generally considered reasonable choices[1]

Approximately a third of patients will fail to respond to the first antidepressant[2]. The usual treatment strategy at this point is to switch to a different SSRI or to trial an SNRI or mirtazapine[1]. Following failure of a second antidepressant, effect sizes from further drug switches, or use of augmenting medications (commonly antipsychotics or mood stabilisers) are modest and diminishing[3]. Patients at this stage of their illness are usually described as suffering from 'treatment-resistant' depression and are beyond the scope of this guideline. Advice from specialist psychiatric services should be sought.

1.3 Treatment of inflammatory bowel disease

Inflammatory bowel disease describes two conditions; ulcerative colitis and Crohn's disease. Ulcerative colitis (UC) affects the colon, Crohn's disease may affect any part of the gastrointestinal tract. Symptoms include pain, diarrhoea, weight loss and tiredness. Patients may also suffer with anaemia, arthritis, uveitis, and jaundice secondary to primary sclerosing cholangitis.

Pharmacological treatments may include 5-ASAs (mesalazine, sulphasalazine), immunomodulators (azathioprine, mercaptopurine, methotrexate, tioguanine), biologics (infliximab, adalimumab, vedolizumab, ustekinumab, golimumab), steroids (prednisolone, budesonide, beclomethasone), or other medicines such as tofacifinib, ciclosporin, tacrolimus, iron supplements, vitamin D, calcium, vitamin B12, and folate.

1.4 Treatment of depression in inflammatory bowel disease (IBD)

Rates of depression in patients with IBD may be twice as high as in the general population[4]. Prevalence of anxiety and depression is higher in those with Crohn's disease than ulcerative colitis[5], and women are more likely to suffer than men[5]. Comorbid anxiety and depression in IBD are associated with worse IBD symptoms (prevalence of anxiety or depression is higher

in patients with active IBD compared with inactive disease[5]) and poorer adherence to medication, as well as increased hospitalization and reduced quality of life[6]. The presence of depression increases the risk of developing IBD [7]; treatment with antidepressants mitigates this risk[7].

Tumour necrosis factor-alpha (TNFα) is known to play a role in Crohn's disease. Research suggests that (in the absence of medical illness) levels of inflammatory markers are raised in depression, and that antidepressants may change the circulating levels of these cytokines[6]. Meta-analysis shows that SSRIs may be associated with a reduction in IL-6 and TNFα levels, with other antidepressants having no effect[8]. Data are conflicting however, with subsequent articles demonstrating TNF-α lowering properties of mirtazapine[9]. How this should be extrapolated to drug choice in patients with pathologically-raised levels of inflammatory markers, as in IBD, is not yet clear. Single case studies describe resolution of the symptoms of Crohn's disease following treatment with phenelzine[10] or bupropion[11]; both drugs that are thought to reduce TNFα by reducing intracellular cAMP[12]. The hypothesis for this mechanism of action directly affecting the symptoms of IBD remains theoretical and is not explored in clinical trials, so should not yet form the basis of decisions to select one antidepressant over another.

Up to 30% of patients with IBD are prescribed antidepressants[4], which may be used to treat depression, anxiety, or the symptoms of the IBD itself. There are few high-quality randomised controlled trials of antidepressants in patients with IBD[13], so decisions on the treatment of depression in patients with IBD are largely based on efficacy and tolerability data from the non-IBD population. It should be noted that the biological symptoms of depression that are measured by standard depression rating scales may not appear to improve on addition of antidepressants due to overlap of these signs with ongoing symptoms of IBD (e.g. Fatigue). Antidepressant choice should be made based on the likelihood of adverse effects that would worsen the symptoms of IBD and/or comorbid conditions, and the likelihood of drug interactions with medicines usually prescribed for IBD and/or comorbid conditions.

1.5 Aims of treatment

The aim of the use of antidepressants to treat depression in patients with comorbid IBD is to provide relief of depressive symptoms, with minimal or no adverse impact on the symptoms of the IBD or interactions with the medications used to treat the IBD. This document does not specifically address the use of antidepressants to treat the symptoms of IBD in the absence of depression, although some principles of drug choice described here may still be relevant.

1.6 General points on antidepressants

1.6.1 Time to response

The rate of improvement in depressive symptoms in response to antidepressant treatment is highest in the first 1 – 2 weeks, reducing from there to the lowest rate during weeks 4 – 6. In clinical practice, antidepressant effects in individual patients are usually seen within the first two weeks[14].

If there is no response by weeks 3 – 4, any latent response is highly unlikely and it is recommended that a treatment switch be considered[2].

1.6.2 Duration of treatment

Antidepressants should be taken for 6 – 9 months after recovery from a single episode of depression. For patients who have had multiple episodes of depression, treatment should be continued for at least 2 years, but probably longer[2].

Time to response	Comment
1-2 weeks	Degree of improvement highest
3-4 weeks	If no response then switch
4-6 weeks	Lowest response rate
6-9 months	After **recovery** of single episode, can be reviewed/stopped.
2 years	After multiple episodes continue for a minimum of 2 years.

Table 1: summary of response times for antidepressants

1.6.3 Toxicity in overdose

As well as higher rates of depression and anxiety[5], IBD is also associated with higher rates of mortality in suicide compared to the general population[15,16]. Antidepressants have differing toxicity profiles if taken in overdose, and this may a relevant consideration when selecting drugs for individual patients. MAOIs (excluding moclobemide) and TCAs (excluding lofepramine) are considered highly toxic in overdose, and venlafaxine is moderately so[17]. Other drugs are comparatively less toxic, but clearly may become more problematic if co-ingested with other substances, or where comorbid physical health issues are present.

2 Choice of antidepressant

2.1 Gastrointestinal (GI) side effects

Serotonin is heavily involved in gastric motility[18]. All drugs that affect serotonin receptors or serotonin levels may therefore affect motility. Additionally, drugs that act on central 5-HT_3 receptors can cause nausea and vomiting. Up to half of patients taking SSRIs or SNRIs may experience GI side effects (abdominal pain, diarrhoea, nausea, dyspepsia) in the first few days and weeks[19]. Most side effects of this nature are dose-related; using the lowest therapeutic dose should always be the aim of treatment. The use of modified-release preparations may help reduce these side effects[20], although data supporting this strategy are not consistent[21]. The aim is to achieve lower peak plasma concentrations and little fluctuation in plasma concentration from minimal to maximal.

Table 2 summarises a large recent meta-analysis[22] comparing gastrointestinal side effects of antidepressants (TCAs were not included). Note that data were restricted to short-term trials; it is not uncommon for gastrointestinal side effects to lessen after the first few weeks. It should also be noted that other analyses do not produce exactly the same ranking[23,24]. Antidepressant choice for individuals should be informed by previous response to medication, predominant gastrointestinal symptoms, the expected interaction of the pharmacology of the antidepressants with these factors, as well as population data from clinical trials such as those presented here.

Nausea and vomiting	Diarrhoea	Constipation
Duloxetine (4.33)	Sertraline (2.33)	Duloxetine (2.58)
Vortioxetine (4.28)	Fluvoxamine (2.29)	Venlafaxine (2.45)
Venlafaxine (3.52)	Escitalopram (1.91)	Sertraline (2.38)
Sertraline (2.78)	Citalopram (1.64)	Paroxetine (2.14)
Fluvoxamine (2.72)	Duloxetine (1.60)	Agomelatine (2.10)
Escitalopram (2.51)	Agomelatine (1.39)	Vortioxetine (1.59)
Paroxetine (2.11)	Paroxetine (1.35)	Bupropion (1.52)
Citalopram (1.85)	Fluoxetine (1.29)	Fluvoxamine (2.14)
Agomelatine (1.77)	Vortioxetine (1.23)	Mirtazapine (1.46)
Bupropion (1.52)	Venlafaxine (1.00)	Citalopram (1.39)
Fluoxetine (1.45)	Bupropion (0.88)	Escitalopram (1.28)
Mirtazapine (0.73)		Fluoxetine (1.00)

Table 2: summary of GI side effects of antidepressants. Odds ratios compared with placebo given in brackets.

Shaded sections are drugs that did not differ from placebo.

Note no data available for mirtazapine and rates of diarrhoea in short-term studies.

2.1.1 Patients with nausea and vomiting

Mirtazapine exhibits antinausea properties due to 5-HT_3 antagonism. All other drugs that affect serotonin availability in the gastrointestinal tract and CNS are associated with nausea and vomiting; TCAs and MAOIs may be preferable to SSRIs and SNRIs for this reason[22]. This effect may also be dose dependent.

Recommendation: mirtazapine.

2.1.2 Patients with diarrhoea

Tricyclic antidepressants slow gastrointestinal transit due to anticholinergic effects, so may be of benefit to patients with diarrhoea. The tertiary amines (amitriptyline, imipramine) are more strongly anticholinergic than the secondary amines (desimipramine, nortriptyline), so have more marked constipating activity. SNRIs may also exert this effect, as may mirtazapine. Although not included in the meta-analysis above, other reviews report low comparative incidence of diarrhoea associated with mirtazapine (6.4%[24]). SSRIs increase gastric motility via serotonergic activity so are best avoided. Agomelatine is associated with low rates of diarrhoea (comparable to placebo) in clinical trials and lacks serotonergic activity, so is unlikely to worsen diarrhoea (or benefit it).

Recommendation: TCA (consider amitriptyline or nortriptyline – see section 2.2), venlafaxine, agomelatine, mirtazapine or bupropion. If SSRI is required, prefer paroxetine or fluoxetine, consider vortioxetine.

2.1.3 Patients with constipation

Constipation caused by antidepressants is secondary to their anticholinergic effects. Tricyclic antidepressants are therefore associated with higher incidence of constipation than other drugs and should be avoided. Paroxetine, mirtazapine and trazodone are also more anticholinergic than other options so should probably be avoided as first line choices, although the meta-analysis referenced above found no difference in rates of constipation between mirtazapine and placebo. SSRIs may increase gastric and small bowel motility due to effects on serotonin receptors, so may be of benefit to those with constipation.

Recommendation: SSRI (not paroxetine or sertraline), mirtazapine (possibly reserve as a second-line option).

2.2 Pain

Antidepressants are used to treat chronic pain (especially neuropathic pain), usually in lower doses than those considered therapeutic for the treatment of depression. Drugs that affect both the serotonin and noradrenaline monoamine systems appear to be more effective[25] – for this reason, TCAs and SNRIs are preferred. Of the TCAs, some authors suggest that the tertiary amines (amitriptyline and imipramine), which inhibit serotonin to a greater degree than their effect on noradrenaline, may be more effective than the secondary amines (nortriptyline) which exert more effect on noradrenaline[26], although this is not found consistently. TCAs and venlafaxine have a NNT for neuropathic pain of 3[27]. Imipramine lacks a good quality evidence base to support use – other options have greater supportive evidence[27].

NICE[28] recommend amitriptyline or duloxetine as antidepressants for the treatment of neuropathic pain, but note that venlafaxine can be used in specialist settings.

	Dose for neuropathic pain	Minimum therapeutic dose for depression[17]
Amitriptyline	25 – 75mg/day[29]	75 – 125mg/day
Nortriptyline	10 – 75mg[30]	75 – 125mg/day
Duloxetine	60 – 120mg[26]	60mg/day
Venlafaxine	> 150mg/day[26]	75mg/day

Table 3: comparison of antidepressants dosages

Note: unlicensed use of nortriptyline, duloxetine and venlafaxine

For patients with comorbid pain and depression not currently taking an antidepressant it is sensible to choose venlafaxine or duloxetine as these options can be used for both indications at similar doses. TCAs are usually well tolerated in the low doses used for pain relief [31] but their side effects (principally those related to anticholinergic effects) may make them difficult to tolerate for patients with pre-existing gastrointestinal disorders at doses required to also treat depressive symptoms.

If patients are taking duloxetine or venlafaxine for pain relief but still experiencing depressive symptoms, the first step should be to optimise dosing; where possible doses should be increased as far as tolerated. If this is unsuccessful or not tolerated, switching to a different antidepressant is preferable (choice should be made based on patient preference, concurrent drugs and other comorbidities and previous response to antidepressants). If the patient does not wish to discontinue the SNRI because it is helpful in providing pain relief, then combination antidepressant therapy may be necessary. The combination of mirtazapine with venlafaxine is supported by the STAR*D study and usually well tolerated[32], although there is a risk of serotonin syndrome. Combination with agomelatine is likely to be safe, but efficacy is not proven and limited to case reports[33]. Further options include augmentation with lithium, quetiapine or aripiprazole[17].

Where patients are already taking low doses of TCAs for pain relief and do not wish to discontinue, a second antidepressant may need to be added in order to treat depression. Combining TCAs with SSRIs or SNRIs presents three problems. Firstly, fluoxetine, paroxetine, and to a lesser extent sertraline, citalopram, escitalopram, venlafaxine and duloxetine inhibit CYP2D6, which is involved in the metabolism of TCAs[34]. Secondly, additive antimuscarinic and cardiac side effects should be expected. Finally, there is an increased risk of serotonin syndrome. Agomelatine lacks the serotonergic, anticholinergic and CYP inhibiting

properties of the other drugs and therefore presents no problems in combination with TCAs. Combining low-dose TCAs with mirtazapine is probably preferable to combining TCAs with SSRIs because it also lacks the risk of serotonin syndrome or CYP inhibition, but is more anticholinergic than agomelatine. The combination of TCA with SSRI or SNRI should only be attempted if other, safer options have been ruled out and should be undertaken with caution. Patients must be aware of the signs of serotonin syndrome.

2.3 Fatigue

It is helpful to first consider the nature of the fatigue, specifically whether **insomnia** is a contributing factor. Agomelatine, a melatonin receptor agonist, improves sleep quality in patients with depression by mimicking the natural rhythm of melatonin release[35]. Mirtazapine reduces sleep latency and improves total sleep time and quality[35,36] due to histaminergic activity. The effect on histamine receptors predominates at lower doses (< 7.5mg); noradrenergic effects become more apparent at higher doses (minimum effective dose for depression is 30mg/day) and drowsiness is reduced (although this is disputed[37]). Trazodone has a hypnotic effect in low doses (25 – 100mg), inducing and maintaining sleep without causing daytime sleepiness due to its short half life (3 – 6h)[38]. Higher doses are needed to treat depression (> 150mg/day) which are likely to cause daytime drowsiness.

For patients are **fatigued without insomnia**, antidepressants with the lower risks of sedation should be selected. Mirtazapine and trazodone should be avoided (but bear in mind that the sedative effects of mirtazapine may dissipate at higher doses), as should duloxetine and TCAs - these agents have greater reports of fatigue and sleepiness than placebo[39]. SSRIs, venlafaxine and agomelatine have a similar incidence of fatigue to placebo in clinical trials so are preferable[39]. Bupropion has a unique mechanism of action in depression, involving dopaminergic and noradrenergic activity. In practice, it has an alerting effect and may therefore be useful in patients struggling with significant fatigue. It is unlicensed for this indication in the UK.

Be aware that conditions such as anaemia, vitamin B12 deficiency, folate deficiency and vitamin D deficiency frequently occur in patients with IBD, and may cause fatigue. These should be investigated and corrected accordingly.

2.4 Patients taking steroids

Depression, along with other psychiatric symptoms (psychosis, mania) is reported by patients taking corticosteroids. Psychiatric side effects of steroid treatment usually have a rapid onset (1 – 2 weeks) and the incidence is dose-related[40]. Risk may be increased by other drugs or conditions that increase the circulating levels of corticosteroids (clarithromycin, hypoalbuminaemia[40]).

The first step in treatment of steroid-induced depression must be, wherever possible, to reduce and/or stop the steroid. Tapering should be slow; psychiatric symptoms can be induced by withdrawal of steroids, especially if this is rapid[40]. If the steroid cannot be withdrawn, pharmacological management of the depressive symptoms may be necessary. No controlled trials are available to guide drug choice. Choice of antidepressant should be based on the usual criteria (patient preference, concurrent medication, comorbidities, previous response).

Patients taking long-term steroids are at increased risk of bone mineral density loss and osteoporosis. Serotonergic drugs can increase the risk of osteopaenia[41,42]. The risk of fracture is higher in a patient with frequent falls, and further increased by concurrent osteopaenia. Data are mostly available for older adults, and should be interpreted cautiously

due to confounding by indication. In general, the effect of the antidepressant on the serotonergic system is the cause of the fracture risk, so SSRIs are best avoided in vulnerable patients[43]. MAOIs (moclobemide) and NaSSAs (mirtazapine) may be preferable, but data are lacking to confirm this.

Note that omeprazole interacts with citalopram and escitalopram, and pantoprazole with escitalopram, in both cases potentially increasing the plasma concentration of the antidepressant and increasing the risk of dose-dependent side effects, including prolonged QTc. Rabeprazole is preferred.

2.5 Nil by mouth

In general, if oral access for drug administration is not possible for a short period of time (**days**), omitting antidepressants is unlikely to present problems. The drug can usually be restarted at the previous dose after the break in treatment (but use lower doses if the patient's medical has changed and they are more vulnerable to side effects). If the treatment break is likely to be longer than this (**weeks**) or the patient shows signs of depressive relapse or antidepressant withdrawal, alternative options may need to be considered. If it is possible to take small volumes of liquid by mouth, citalopram drops may be used (20mg is contained in 8 drops, equivalent to 0.4ml).

Other antidepressant options that are easily available in the UK (although unlicensed and with efficacy data limited to case reports) are to give the liquid preparation of fluoxetine sublingually (20mg/5ml), crush amitriptyline tablets and allow them to be absorbed buccally, or use orodisperisble mirtazapine for absorption in the buccal cavity[44]. Plasma concentrations are likely to be lower than for conventional oral administration; levels can be taken although are of use more to confirm that some systemic absorption has taken place rather than to establish whether a therapeutic level has been achieved (what constitutes a therapeutic plasma level has not been agreed for most antidepressants and is likely to be different for individuals). For patients who have been receiving sublingual or buccal medication for a week or two with no response, checking the plasma level is a reasonable step to take to establish whether non-response is due to lack of absorption or treatment failure. Note that orodispersible preparations of drugs such as mirtazapine and olanzapine are not designed for buccal absorption – rather, the drug disperses into saliva which must be swallowed, allowing gastrointestinal absorption.

A further option is to use intramuscular flupenthixol decanoate – this is an antipsychotic depot injection with antidepressant properties. When used at low doses (5 – 10mg/2 weeks) it is well tolerated. Onset of action is not immediate – several weeks may be required to achieve therapeutic plasma levels. Asenapine, an atypical antipsychotic, lacks data to support use in unipolar depression (and is not licensed for this indication) but is effective in the treatment of depression in bipolar disorder. It has the significant advantage of being designed to be entirely absorbed in the buccal cavity.

There are several non-oral preparations of antidepressants that can be obtained but usually not without some delay. Transdermal selegiline is licensed in the USA and can be imported for use in the UK. Intravenous clomipramine is a European preparation that can also be obtained. Intravenous citalopram is an unlicensed preparation that can be requested directly from the manufacturer.

Finally, esketamine nasal spray may have a particularly useful role for patients who are unable to take oral medications. At the time of writing it had not been recommended for use in the NHS by NICE, although it is a licensed medication in the UK. There is a growing evidence

base for the use of intravenous, subcutaneous or sublingual ketamine for depression; this may be easier to obtain.

2.6 Management of patients with a short bowel

Drug absorption in patients with gastrointestinal disease is affected by several factors, including gastric emptying and transit time, and the length of intestine available for absorption[30]. The latter is of particular importance. The small intestine (duodenum, jejunum and ileum) is the most important site for drug absorption, and within this the upper portion (duodenum and jejunum) play the largest role [45]. Slowing the rate of gastric emptying reduces the rate of intestinal absorption[45] - administering medication on an empty stomach with water improves this process. Aqueous solutions are more rapidly absorbed than solid dosage forms or suspensions[45].

If patients have had a portion of their intestines removed, or for other reasons drug absorption is expected to be limited in some or all of the GI tract, concerns are often raised about whether antidepressants will be absorbed into the systemic circulation. Predicting the effect of these conditions on antidepressant absorption and efficacy is difficult, and will differ for each patient depending on the extent of the intestinal resection. Plasma concentrations may be useful in elucidating whether any absorption is occurring, but as previously stated the relationship between plasma level and effect is not well established for most antidepressants. If it is possible to take a plasma level before surgery this may be helpful for comparison. In Table 4, plasma concentration ranges are given where they are available. Note that these should not be interpreted as evidence-based therapeutic ranges; in many cases they are simply plasma levels measured at steady state for licensed doses, and the table below gives the broadest ranges of plasma concentrations provided in the literature. Reported ranges frequently vary widely between studies and between patients. Observation of the patient response and comparison to levels achieved during a period of effective symptom control is much more important.

Drug	Range (trough, mcg/L))
Amitriptyline[17,46]	80 –200
Nortriptyline[17,47]	50 – 170
Fluoxetine[46,48]	80 – 300
Imipramine[46,47]	175 – 350
Mirtazapine[49]	5 – 100
Sertraline[20,46,50–52]	10 – 50
Citalopram[46]	30 – 130
Escitalopram[46]	15 – 80
Clomipramine[53]	100 – 250
Moclobemide[46]	300 – 1000
Paroxetine[54]	20 – 120
Trazodone[46,55]	260 – 1500
Venlafaxine[56]	10 - 200
Trimipramine[46]	150 - 350
Mianserin[46]	15 - 70
Vortioxetine[57]	9 - 33

Table 4: summary of plasma concentrations

Modified-release drug formulations should be avoided. Soluble, liquid, or uncoated formulations are preferred. Antidepressants available in licensed soluble or liquid formulations are listed below. Other drugs may be available as unlicensed ‘special’ liquid formulations.

Drug	Formulation
Escitalopram	Oral drops 20mg/ml
Imipramine	Sugar free solution 25mg/5ml
Amitriptyline	Sugar free solution 25mg/5ml, 50mg/5ml
Lofepramine	Sugar free suspension 70mg/5ml
Mirtazapine	Orodispersible tablet 15mg, 30mg, 45mg Sugar free solution 15mg/ml
Nortriptyline	Sugar free oral solution 10mg/5ml, 25mg/5ml
Paroxetine	Suspension 20mg/10ml
Tranylcypromine	Sugar free solution 50mg/5ml, 100mg/5ml
Citalopram	Oral drops 40mg/ml
Fluoxetine	Sugar free solution 20mg/5ml
	Dispersible tablet 20mg

Table 5: summary of formulations available

Little is known about the exact site of absorption of antidepressants. There are no clinical trials of administration of antidepressants to patients with short bowels, and few case reports. In the absence of data to guide drug selection based on pharmacokinetics, the following principles of prescribing are recommended.

For patients **already established on an antidepressant which has been effective**, maintain this treatment at the pre-surgery dose, switching to a liquid preparation if possible and converting modified release preparations to the equivalent immediate release. Observe response (preferably over several weeks). If relapse occurs (or symptoms of antidepressant withdrawal emerge) then increase the dose to no more than the licensed maximum. This is preferably guided by comparing plasma concentrations to pre-surgery levels, but if these are not available then a dose increase in their absence is reasonable. If no response is seen after a further 1 – 2 weeks, plasma levels are strongly recommended before any consideration of increasing the dose beyond the licensed maximum. If a plasma level at this stage shows lower levels than achieved on a previously effective dose, consideration may be made of increase the dose beyond the license with the aim of achieving the previously effective plasma concentration. If this is not effective (assess over 1 – 2 weeks), not possible, or not acceptable to the patient or prescriber, then the antidepressant should be switched. Switching to another drug with a similar pharmacological activity is rational if response was good to the pre-surgery antidepressant.

For patients **not already taking an antidepressant**, drug choice should be based on the usual factors (patient choice, comorbidities, concurrent medication, previous response to antidepressants) and availability of the chosen agent in liquid form. Dosing should be commenced as normal and response assessed over 2 – 4 weeks. If no response is observed, a plasma level is recommended to establish non-absorption versus non-response. If the plasma level is low, increase the dose to the licensed maximum. If no response is observed, the drug should be switched.

2.7 Drug interactions

Mirtazapine + immunosupressants

Bone marrow depression (presenting as granulocytopaenia or agranulocytosis) has been reported rarely (0.1%[58]) during treatment with mirtazapine. It is usually reversible on treatment cessation, but has been fatal (more likely in those over 65)[29]. The combination of mirtazapine with other agents associated with bone marrow depression is not contraindicated and there are no published reports of adverse effects of the combination, but knowledge of the potential

for an additive risk may be useful. Regular blood monitoring is recommended routinely for patients taking immunosuppressants.

Tofacitinib + CYP inhibitors

Tofacitinib requires dose adjustment when administered with potent inhibitors of CYP3A4, or with moderate inhibitors of CYP3A4 in combination with potent inhibitors of CYP2C19[29]. This affects fluvoxamine (CYP3A4 and 2C19 inhibitor) and fluoxetine (CYP3A4 inhibitor).

Ciclosporin/tacrolimus + CYP3A4 inhibitors

Inhibitors of CYP3A4 may increase plasma levels of ciclosporin and tacrolimus[29]. Theoretically this may include fluvoxamine and (to a lesser extent) fluoxetine; there are small numbers of case reports describing this interaction for ciclosporin and a small case series demonstrating no change in ciclosporin levels with concurrent fluoxetine. Ciclosporin and tacrolimus plasma levels are measured regularly in practice; ensuring this is done when starting, stopping, or altering doses of these antidepressants is recommended.

Tacrolimus + QT prolonging drugs

Tacrolimus has been associated with QT prolongation. Concurrent use with other agents that also increase the QT interval may increase the risk; this includes antidepressants. Periodic ECGs are recommended[58] and TCAs avoided if possible.

3 Counselling

- Patients should remain at the heart of all treatment decisions and be fully involved in decisions regarding choice of antidepressant.
- Agree with the patient the symptoms of their depression they are aiming to treat with the antidepressant. Discuss how to measure treatment success/failure based on this.
- Patients can be reassured that for most people (two thirds), the symptoms of their depression are reduced, or entirely eliminated, with the first antidepressant they try.
- The greatest effect on symptoms is seen in the first one to two weeks of treatment. They will not need to suffer weeks waiting for relief from symptoms. If they have no symptom relief within a few weeks of treatment, their medication can be changed.
- It is recommended that most people continue to take their antidepressant for 6 – 9 months after their symptoms subside. Some people, especially those who have had repeated episodes of depression, should take treatment for at least two years, or possibly longer.
- Antidepressants are not addictive. Unlike addictive substances, people do not need to take increasing doses of antidepressants to get the same effect, and do not crave antidepressants. They may, however, cause some withdrawal symptoms for some people on stopping. These can be reduced or eliminated by stopping slowly.

3.1 Patient information sources

- Royal College of Psychiatrists: *https://www.rcpsych.ac.uk/mental-health/problems-disorders/depression*
- Mind *https://www.mind.org.uk/information-support/types-of-mental-health-problems/depression/about-depression/*

- South London and Maudsley patient information leaflets: *https://www.slam.nhs.uk/patients-and-carers/medication*

4 Contacts

Siobhan Gee, principal pharmacist for liaison psychiatry: 07773108081; Siobhan.Gee@slam.nhs.uk

Psychiatric Medicines Information: 0203 228 2317; pharmacy_staff_medicines_information@slam.nhs.uk

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