Guidance on the Use of Antidepressants in Children and Adolescents

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1. MANAGEMENT OF DEPRESSION

1.1 Introduction & Summary

1.1.1 Antidepressants are used for a variety of presentations in children and adolescents, however few antidepressants are licensed for use in childhood disorders and the evidence base is poor.

Prescribers must remain aware that recommendations for the use of medication other than fluoxetine are based on paper review and subsequent interpretation is not supported by the Medicines and Healthcare Products Regulatory Agency (MHRA). The CSM in June, September and December 2003 issued advice stating:

“Only fluoxetine has been shown in clinical trials to be effective in treating depressive illness in children and adolescents, although it is possible that, in common with the other SSRIs, it is associated with a small increased risk of self-harm and suicidal thoughts. Overall, the balance of risks and benefits for fluoxetine in the treatment of depressive illness in under-18s is judged to be favourable”

Therefore, prescribing beyond fluoxetine places the prescriber at greater risk with regard to accountability and liability for treatment outcome. However it is recognised that specialists may sometimes decide to use other antidepressants in response to individual clinical need. It is therefore strongly recommended that if prescribers are considering the use of medication beyond fluoxetine, sertraline or citalopram (the latter two being off-licence but with a reasonable evidence base), they seek a second opinion from a consultant/associate specialist colleague and/or input from the specialist CAMHS pharmacist before proceeding. The use of an antidepressant beyond those previously highlighted requires appropriate written consent.

1.1.2 Antidepressants should only be used in moderate to severe depression. Psychological therapies should be the cornerstone of treatment with the use of antidepressants being restricted to use after psychological therapies are initiated unless such therapies are refused. If psychological therapy is trialled and proves insufficient in the resolution of depressive symptoms then consideration may be given to initiation of antidepressant medication.

1.1.3 Information leaflets for antidepressant medication are available in both a young person (easy read) and adult format. These can be accessed at www.choiceandmedication.org.uk/sussex

1.1.4 The Trust advises the use of consent forms, particularly when the antidepressant is off licence. These can be accessed at: http://www.sussexpartnership.nhs.uk/gps/med-info/med-docs

1.1.5 Use in children and adolescents under 18 years of age: Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. NICE CG28 guidance suggests weekly contact with the child or young person and their parent(s) or carer(s) for the first 4 weeks of treatment.

1.2 Choice of antidepressant

1.2.1 Fluoxetine should be the first antidepressant considered for prescribing in children and adolescents due to this antidepressant having the best evidence base available, whilst being licensed in those aged 8 years and over.

1.2.2 If a second line pharmacological therapy after fluoxetine is required then sertraline or citalopram are recommended. These should only normally be used when the following criteria have been met:

- The patient and their parent(s)/carer(s) have been provided with appropriate written information regarding rational for treatment, benefits and risks, delay in onset of effect, time course of treatment, possible side-effects, and the need for adherence to the treatment regime. Provision of the latest patient information is available from...
http://www.sussexpartnership.nhs.uk/service-users/what-happens/medication and any advice from the MHRA subsequent to this publication should also be considered.

- The depression is sufficiently severe and/or causing sufficiently serious symptoms to justify the trial of another antidepressant.
- There is clear documented evidence of a fair trial of fluoxetine in combination with psychological therapy.
- There has been a reassessment of the likely causes of the depression, of any possible treatment resistance and other potential diagnosis e.g. bipolar disorder or substance misuse.
- The initiating prescriber is a consultant or associate specialist child and adolescent psychiatrist.
- The child/young person and/or someone with parental responsibility (where appropriate) has signed an appropriate consent to treatment form.

1.2.3 The following medications should not be used:
- Paroxetine
- Venlafaxine
- Tricyclic antidepressants
- Agomelatine
- Monoamine oxidase inhibitors
- St. Johns Wort

1.2.4 If the patient is taking St John’s Wort (over the counter purchase):
- Inform the patient and their parent(s)/carer(s) that there are no clinical trials regarding the use of St John’s Wort in children or young people, that the drug has a relatively unknown side-effect profile and that the drug has several significant drug interactions.
- Advise discontinuation of St John’s Wort and monitor for recurrence or worsening of depression.

1.2.5 The data for individual antidepressants is conflicting.

From the limited data available, fluoxetine and possibly sertraline and citalopram have demonstrated consistent efficacy. The Cochrane review by Hetrick et al. evaluated 19 studies of newer generation antidepressants for depressive disorders in children and young people aged 6–18 years. The review included 5 trials of fluoxetine, 2 trials of sertraline, 2 trials of citalopram, 4 trials of paroxetine, 2 trials of venlafaxine, 2 trials of escitalopram and 2 trials of mirtazapine. Subgroup analyses of individual therapies found a significant impact of treatment with fluoxetine with regard to reduction in depressive symptoms (p<0.00001), remission or response (RR=1.47, p=0.032; 4 studies). Treatment with citalopram, mirtazapine or paroxetine did not have a significant impact on any of the measures reported. For sertraline, the only outcome showing a significant impact of treatment with fluoxetine with regard to reduction in depressive symptoms (p=0.02; 2 studies) and improvement in functioning, (p=0.029; 2 studies), but in no other outcomes. For venlafaxine, there was no evidence of a beneficial effect but an increased risk of suicide-related outcomes (RR=12.93, p=0.013; 1 study).

1.2.5.1 Fluoxetine

Currently fluoxetine is the only selective serotonin reuptake inhibitor (SSRI) licensed in the United Kingdom for treatment of major depressive disorder in children and adolescents 8 years and older to treat moderate to severe major depression that is unresponsive to psychological therapy after 4–6 sessions, only in combination with a concurrent psychological therapy. Fluoxetine is the only SSRI that has evidence that the benefits outweigh the risks and is approved for use in this population.
1.2.5.2 Sertraline

Some efficacy for sertraline has been suggested by two 10 week long RCTs\(^8\), which when combined included a total of 364 young people. The percentage of young people responding in the sertraline and placebo groups was 69% and 59% respectively\(^9\). Data from the sub-group analysis of children on depressive disorder symptom severity scores on the CDRS-R showed no statistically significant differences in scores between the sertraline and placebo treated groups (treatment effect -2.34, 95% CI -7.01 to 2.33). However for adolescents, depressive disorder symptom severity scores were significantly lower in the group treated with sertraline (treatment effect -4.56, 95% CI -8.79 to -0.32). When these sub-groups were combined, depressive disorder symptom severity scores were statistically significantly lower in the group treated with sertraline (Treatment effect -3.56, 95% CI -6.69 to -0.42). However, if the trials are considered separately there was no statistical difference in the percentage of young people responding between treatment and placebo groups (RR 1.17, 95% CI 1.00 to 1.36).

1.2.5.3 Citalopram

To date there have been two published RCTS of citalopram\(^10\) & \(^11\). Both of these trials reported statistically significant increase in the percentage of those who responded in the citalopram group compared to the placebo group (RR 1.30, 95% CI 1.02 to 1.67), with the percentage of participants responding in the citalopram groups varying between 36% and 46% and in the placebo groups between 24% and 38%. However the CDRS-R scores when combining the two trials did not demonstrate significantly lower results in the group treated with citalopram compared to placebo\(^7\) & \(^9\).

1.2.5.4 Escitalopram

Escitalopram is licensed in the USA for the treatment of moderate to severe depression in children and adolescents, although the evidence base for such use is limited\(^12\). The evidence available in children and adolescents is based upon two 8 week studies compared with placebo. The first of these\(^13\) witnessed no improvement in symptoms CDRS-R scores for the whole treatment group, but when considering just adolescent patients there was a significant improvement in CDRS (\(p = 0.047\)), whilst the second saw significant improvement in the escitalopram group relative to the placebo group at endpoint in CDRS-R score (\(p = 0.022\))\(^14\). Therefore since the efficacy for use in children and adolescents depression has not been consistently demonstrated such use is not routinely recommended

Currently escitalopram is not approved for use in primary care in West Sussex for treatment of depression in adults, other than by ‘named patient application’ at the discretion of the clinician.

1.2.5.5 Paroxetine/Venlafaxine

To date the evidence available suggests that both paroxetine and venlafaxine have little impact on response to treatment, symptom levels, functional status, or clinical improvement\(^4\) & \(^6\). There is evidence that both paroxetine and venlafaxine are more likely than placebo to bring about serious adverse effects, and limited evidence of increased risk of suicidal behaviour/ideation and early discontinuation from treatment because of adverse events or other reasons\(^4\) & \(^6\). Therefore these medications should not be used in patients under the age of 18 years.

1.2.5.6 Mirtazapine

Mirtazapine (a presynaptic alpha-2 antagonist) is unlicensed in the UK and the USA for the treatment of depression in children and adolescents. The evidence base for use of mirtazapine in the treatment of depression in children and adolescents is limited to three clinical trials\(^15\) & \(^16\). Two of these were randomized placebo-controlled trials and provided evidence of a lack of efficacy of mirtazapine in children and adolescents, and there were also concerns around safety. The third clinical trial showed efficacy but had limitations of open label design and being conducted in a small number of patients\(^15\) & \(^16\). Hence the safety and efficacy of mirtazapine in children and adolescents has not been currently demonstrated, and should only be prescribed in exceptional circumstances.
1.3 Indications for initiating an antidepressant

1.3.1 Antidepressants should not be considered first-line for the treatment of major depression in children and adolescents, but should be considered when other treatment has failed or there is a history of moderate to severe recurrent depression.\textsuperscript{2,3}

1.3.2 For major depressive disorder in children and adolescents:
\begin{itemize}
\item Consider CBT, or alternative psychological therapies, for those not responding to initial structured supportive treatment
\item The choice between CBT/psychological therapies and an SSRI in adolescents should be based on individual assessment and availability of treatments
\item Combining CBT and newer antidepressants in moderate to severe depression may improve global functioning in the short term compared to either therapy alone.
\end{itemize}

1.3.3 Calati et al.\textsuperscript{17} conducted a meta-analysis in patients with moderate to severe depression comparing combined CBT and antidepressant medication with the same antidepressant alone over 12 weeks of treatment. A total of 5 RCTs (n=1621) were included, comprising 4 studies of major depressive disorder and 1 study (n=488) of anxiety disorder. Treatment with combination therapy was associated with significantly improved CGAS score, (p<0.0001); a sensitivity analysis of those with major depressive disorder only also showed a significant difference (p=0.002).

1.3.4 A Cochrane review by Cox et al.\textsuperscript{18} evaluated the use of psychological therapies compared with antidepressant medication, alone and in combination, for the treatment of moderate to severe depression in children and young people. Ten RCTs (n=1235) using standardised criteria were included in the review, involving patients 6–18 years with a diagnosis of major depressive disorder. Combined psychological therapy and antidepressant medication was compared with antidepressant medication alone in 4 studies (n=618), where there was no significant differences in remission rates, dropouts or suicidal ideation, post-intervention or after 6–9 months. Combined psychological therapy and antidepressant medication was compared with psychological therapy alone in 2 studies (n=265). There were no significant differences in remission rates, dropouts or suicidal ideation, post-intervention or after 6–9 months.

1.4 Antidepressants & Suicidality

1.4.1 The use of antidepressants in children and adolescents has been the subject of much controversy with regards the risk-benefit balance and the relative difference between individual drugs.\textsuperscript{3,4}

1.4.2 When prescribing the clinician should be aware of the increased incidence of deliberate self harm in adolescents and young adults. Smaller antidepressant-placebo differences have been shown when treating depression in children and adolescents compared to those in adults.\textsuperscript{6}

1.4.3 Simple pooling of all antidepressants shows a significant overall benefit for antidepressants (pooled data from 18 RCTs), with an Odds Ratio (OR) of 1.52.\textsuperscript{6} SSRIs as a group were shown to be effective (OR 1.84). Advantage for TCAs was only shown for continuous measures and not responder analysis.\textsuperscript{6}

1.4.4 The risk of clinically significant suicidal behaviour was shown to be highest in the month before starting antidepressant treatment and in the first few weeks of treatment, and declined thereafter with significantly higher rates seen in adolescents compared with adults. There was no increase in suicide or suicide attempt seen with SSRIs compared with other antidepressants in adolescents or adults. A meta-analysis of 27 RCTs of SSRIs use in children and adolescents showed no completed suicides, but a small significant increase in suicidal thought and self harm with SSRIs compared with placebo (NNH = 143).\textsuperscript{19}

1.4.5 Hence although depressive episodes carry their own risk of suicidal thinking, there may be a small increase in suicidal ideation on initiating antidepressant therapy and therefore there is an increased need for extra monitoring when commencing antidepressant medication.
1.5 Monitoring

1.5.1 Prior to commencing medication, it is advisable to enquire about and document baseline symptoms that might subsequently be interpreted as side-effects of medication. Patients and their parent(s)/carer(s) should be informed to make urgent contact with their doctor if there are any signs of new symptoms upon the initiation of antidepressant therapy. For an antidepressant side effect (ASEC) monitoring form please see:  http://www.sussexpartnership.nhs.uk/gps/med-info/med-docs/finish/2050/7881

1.5.2 Arrangements should be in place to carefully monitor for adverse drug reactions especially increased suicidal thinking and hostility (e.g. weekly for the first four weeks of treatment) and to fully record findings in the clinical notes.

1.5.3 Patients must be carefully monitored for suicidal behaviour, self-harm or hostility and overly elevated mood particularly during high risk periods such as at the beginning of treatment and changes of medication. For further information please see the Trust Guidance on the use of Antidepressants located at http://www.sussexpartnership.nhs.uk/gps/med-info/med-docs/finish/2030/7782.

1.5.4 Monitoring should be conducted by the psychiatrist, the clinician delivering psychological therapy and also the patients family. A maximum of one week’s medication supply per prescription should be considered for those assessed at risk.

1.6 Duration of Treatment

1.6.1 The TADS trial showed no significant loss of efficacy over one year of treatment, and 86% of adolescents treated with fluoxetine and CBT continued to demonstrate noticeable improvements19 A second trial demonstrated receiving maintenance treatment with fluoxetine over a 6-month period prevented relapse in comparison with placebo21. Therefore, following NICE guidance to continue treatment for a minimum period of 6 months, after full remission, is clinically appropriate. After the treatment period, medication should be phased out over six to twelve weeks with the exact dose and dose reductions being titrated against the level of discontinuation symptoms4.

1.6.2. A subgroup analysis of the TADS trial22 suggested that young people with depression in families with high levels of parental marital discord may benefit from treatments that include medication (fluoxetine alone or combined with CBT). This is in contrast to families with low parental marital discord, where treatment of young people with depression with fluoxetine alone or CBT alone was no more effective than placebo.

1.7 Age specific response to antidepressants

Whittington et al (2004)23 showed a significant benefit for SSRIs and other newer antidepressants over placebo for adolescents (62% Vs 29% response, NNT 7-8). For younger children (5-12 years) no significant statistical benefit over placebo (65% Vs 58%) was shown. However, if the data for fluoxetine is taken alone, this shows a significant benefit for both age groups (NNT =5). Therefore, although a range of SSRIs have been shown to be beneficial in some patients in the over 12 years age group, when treating under this age fluoxetine is the only antidepressant with a robust evidence base.

1.8 Further Treatment Options

1.8.1 There is a general lack of evidence for next-step treatments in children and adolescents, and for the prevention of relapse in children and adolescents8.

1.8.2 The Treatment of Resistant Depression in Adolescents24 (TORDIA) trial included 334 young people with clinically significant depression that had not responded to at least 4 weeks of treatment with fluoxetine 20 mg or equivalent SSRI, with the final 4 weeks at a dosage equivalent to 40mg of fluoxetine, unless this dose could not be tolerated. Participants were randomised to 1 of 4 treatment groups: monotherapy with a different SSRI from that previously used (citalopram, fluoxetine or paroxetine); monotherapy with venlafaxine; combination therapy with SSRI and CBT; or combination
therapy with venlafaxine and CBT. The results found that treatment with venlafaxine was not superior to treatment with SSRIs in achieving remission and that initial response at 12 weeks predicted a greater than threefold increased likelihood of remission, with the clinical course of those who eventually remitted had already begun to diverge by 6 weeks of treatment.

A high level of abuse was reported in this study (24.8% of either physical, sexual or both), which impacted on the results achieved. Those patients with a history of physical abuse showed significantly lower response to combination treatment than medication alone, whilst for those with a history of sexual abuse, there was no significant effect on results obtained. Among participants with no history of abuse, the response to treatment was significantly higher with combination therapy (62.8%) than medication alone (37.6%; odds ratio [OR]=2.8, p<0.001)\textsuperscript{25}.

1.8.3. Where psychotic features are present consideration may be given to augmenting the current antidepressant treatment plan with an atypical antipsychotic. Please refer to the Trust antipsychotic guidelines for information regarding licensing, monitoring and dosing, which can be accessed at: http://www.sussexpartnership.nhs.uk/clinical/medication/docs/camhs/prescribing/?assetdetesctl5850444=36729

1.9 Electroconvulsive Therapy (ECT)

1.9.1 ECT should only be considered for young people (12 to 18 years) with very severe depression and either life threatening symptoms or intractable and severe symptoms that have not responded to other treatments\textsuperscript{2}. The Mental Health Act (2007) legislation requires that strict procedures are adhered to with second opinion assessment essential.

1.9.2 **ECT must not be used in the treatment of depression in children under 12 years of age.**

2. MANAGEMENT OF ANXIETY DISORDERS

2.1 Most adult patients suffering from anxiety disorders describe an onset of symptoms within childhood or adolescence. Many adolescents are significantly disabled by persistent, distressing and severe anxiety symptoms\textsuperscript{26}.

2.2 The United Kingdom Committee on Safety of Medicines, have advised that the risks are less when treating anxiety with antidepressants as opposed to depression largely because the risk of self-harm is less, and the therapeutic benefits greater. However careful monitoring is still advised, due to possible uncertainty around patient diagnosis or co-morbid depression\textsuperscript{26}.

2.3 The British Association of Psychopharmacology (BAP) anxiety guidelines advise reserving pharmacological approaches for patients unresponsive to evidence based psychological therapies\textsuperscript{26}.

2.4 If pharmacological management is deemed appropriate and necessary, SSRIs are a first-line choice but have a limited evidence base\textsuperscript{26}.

2.5 There have been comparatively few controlled trials of psychotropic medications in children and adolescents. From the limited data available SSRIs and clomipramine appear efficacious in the treatment of Obsessive Compulsive Disorder (OCD) and paroxetine in social phobia\textsuperscript{26}. Despite the data available, clomipramine and paroxetine should generally be avoided due to side effects and lack of experience.

2.6 The patient response and rate of remission is similar in adult and child/adolescent populations\textsuperscript{26}.

2.7 Benzodiazepines and tricyclic antidepressants should be avoided due to increased likelihood of adverse effects\textsuperscript{26}.

2.8 Consider careful dosing in relation to age and size of patient, with careful monitoring of adverse effects taking into consideration that children and adolescents may find it difficult to describe them\textsuperscript{26}.
3. SUGGESTED DOSING

3.1 Fluoxetine\textsuperscript{27,28}:
Licensed for children and adolescents aged 8 years and over, for treatment of moderate to severe depression unresponsive to 4-6 sessions of psychological therapy, or severe depression in combination with psychological therapy.

The starting dose is 10mg either as 2.5ml fluoxetine liquid daily or as one 20mg capsule on alternate days, increased to 20mg (usually capsules) after 1-2 weeks if necessary. Maximum licensed dose is 20mg, with doses above this up to a maximum of 60mg normally reserved for OCD symptoms and also bulimia nervosa (both off-licence indications).

3.2 Citalopram\textsuperscript{27}:
Major depressive disorder (off-licensed indication) - Children and adolescents aged 12-18 years: Initially 10mg once daily, increased if necessary to 20mg over 2-4 weeks. Maximum, 40mg daily.

3.3 Escitalopram\textsuperscript{27}:
Depression (off-licence in the UK – licensed in the USA): Children and adolescents aged 12-18 years: Initially 10mg daily, increased if necessary to 20mg daily after 2-4 weeks.

3.4 Sertraline\textsuperscript{27}:
Licensed for treatment of children and adolescents aged 6-18 years, with obsessive compulsive disorder:

Years 6-12: Initially 25mg daily, increased to 50mg daily after one week. Further increased if necessary in steps of 50mg at intervals of at least 1 week. Maximum daily dose of 200mg.

Years 13-17: Initially 50mg daily, increased if necessary in steps of 50mg over several weeks. Usual dose range 50-200mg.

Depression (off-licence): 12-18 years of age: initially 50mg once daily increase if necessary in steps of 50mg daily at intervals of at least a week: max 200mg daily.

3.5 Mirtazapine\textsuperscript{29}:
Depression (off-licence): Initially 15 daily, increased after 2-4 weeks according to response to 30 mg daily at bedtime. Further dose increases after 2-4 weeks according to response, with a maximum of 45 mg daily as a single dose at bedtime.
4 REFERENCES


8. Hetrick SE, Merry SN, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents (Review) Cochrane Database of Systematic Reviews 2009; vol 1


