NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr David Coghill

Name of your organisation: Royal college of Psychiatrists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ✓ **(member Royal College of Psychiatrists)**
- other? (please specify)

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What is the expected place of the technology in current practice?

Within the NHS acute manic and mixed episodes occurring within the context of bipolar 1 disorder in children and adolescents are generally treated by child and adolescent psychiatrists with support from the broader multidisciplinary child and adolescent mental health team (e.g. nurses, clinical psychologists, occupational therapists). There is some regional variation at the upper age range (16 – 18 years) with respect to transition to adult mental health services. In some regions paediatricians treating patients with ADHD have started to initiate treatments appropriate for bipolar 1 to individuals with ADHD and severe mood dysregulation who would not meet criteria for bipolar 1 at full assessment. This can result in patients receiving inappropriate treatment. Across the UK there is variation in practice between child and adolescent psychiatrists with respect the treatments offered this reflects; differing levels of experience and training in bipolar disorder; a lack of quality psychoeducation materials; the broad range of interpretations available to clinicians when implementing current NICE guidance (that requires a downward extrapolation of adult recommendations to children and adolescents); differing interpretations of the available evidence with respect pharmacological treatments.

Current alternatives to aripipazole centre include several medications but it should also be noted that psychoeducational approaches and supportive psychological therapies make an important contribution to overall care. These last two approaches are not controversial and are relevant to all cases however they are also very limited in their effectiveness and would not be appropriate as monotherapies. Of the current medication approaches only lithium has marketing authorisation. Lithium is however associated with a range of practical limitations (e.g. need for pre and post treatment blood tests, narrow therapeutic window and significant adverse effects). Other alternatives include valproate and various antipsychotics (e.g. aripiprazole, olanzapine, quetiapine, risperidone,). Each can be considered as a monotherapy or in combination. Usually a monotherapy would be considered first followed by combination treatments where response is inadequate.

At present aripiprazole should only be initiated in children and adolescents by a psychiatrist with age appropriate training. It is acceptable for continued care being managed within a shared care arrangement between primary and secondary care as long as the secondary care physicians are adequately trained and retain a primary role in directing care. Best care will be given by a multidisciplinary team that includes psychiatry as a key member.

Very little is known about bipolar disorder in those with significant intellectual impairment. Such cases are likely to be complex to manage and may show differential responses to medication. It is appropriate that this assessment specifies manic and mixed episodes. These are associated with bipolar 1 disorder. As described in the current NICE guidance bipolar 1 is rare in preadolescents but when it does occur it is similar to adolescent bipolar 1 and can be reliably diagnosed. On the other hand the validity of bipolar 2 and bipolar NOS are much less well established in children and adolescents and their diagnosis should be avoided. It is

important that this assessment makes this clear. In addition samples that include high rates of comorbidity with ADHD should be regarded with caution as, even in child samples, this is not typical of bipolar 1 and is likely to represent a sample with bipolar 2 or bipolar NOS.

Whilst aripiprazole and the other 2nd generation antipsychotics are not yet available under license for children and adolescents with bipolar disorder they are used by child and adolescent psychiatrists.

The only evidence based guideline I am aware of is that developed by NICE and which is due for revision. This was a well-developed guideline that is now however out of date due to the publication of several relevant clinical trials. The only other UK guidelines are those of the British Association of Psychopharmacology. There are consensus based guidelines. The BAP guidelines are very similar to those from NICE. They are also due for revision. The American Academy of Child and Adolescent Psychiatrists guidelines (Kowatch et al. 2005) are also consensus based. They contain the most detailed treatment algorithms and whilst these are helpful to some degree the lack of an evidence base is of concern.

The advantages and disadvantages of the technology

Whilst most of the medications noted in the first section is supported by some degree of RCT evidence this is not extensive and generally limited to 1 or 2 trials per drug. For lithium, the only licensed medication for bipolar disorder in this group There are currently no prospective, double-blind, placebo-controlled studies of adequate statistical power. The evidence for valproate is rather weak and studies have reported mixed findings with some positive and some negative findings. It also seems that the effect size associated with valproate (about 0.24) is lower than that for 2nd generation antipsychotics (see below). With respect the 2nd generation antipsychotics evidence from short term RCTs suggests that they are efficacious at reducing the symptoms of mania (as measured by the Young Mania Rating Scale) and that the various drugs have similar effect sizes (aripipazole ES vs. placebo 0.9 – 1.2; olanzapine 0.8, quetiapine n/a; risperidone 0.9 – 1.1; ziprasidone 3.7) and NNT (for YMRS response to aripiprazole vs. placebo at endpoint = 3.6; olanzapine 3.8, quetiapine 4.2; risperidone 3.0). These have been described in several reviews all of which conclude that current evidence does not allow differentiation with respect efficacy (e.g. Suddas et al European Neuropsychopharmacology 2011 21, 600–620; Correll et al. J Clin Psychiatry. 2011 72:655-670; Singh et al. Drugs. 2010 70: 433–442).

There have been several direct comparison. There was no difference between quetiapine and valproate with respect degree of symptom reduction, however quetiapine was associated with a greater rate of remission (60% vs. 28%, p=0.02). One study compared risperidone with both valproate and lithium (Geller 2012). With respect response rates risperidone was superior to lithium (68.5% vs 35.6%, P.001) and valproate (68.5% vs 24.0%, P.001) while there were no differences between lithium and valproate.

Each of the second generation antipsychotics does however have a distinctive adverse effect profile. As a group he main adverse effects are; weight gain, hyperprolactinaemia, sedation, neurological effects including extrapyramidal side effects, akathisia and neuroleptic malignant syndrome and cardiovascular effects. The profile of adverse effects in children and adolescents seems to be similar to that found in adults. Most data comes from short term trials and there is very little evidence pertaining to long term use. In a clinical trial for child and adolescent bipolar disorder aripiprazole was associated with somnolence (NNH vs. Placebo = 5.1), extrapyramidal disorder (NNH = 6.0), akathisia (NNH = 13.2) salivary hypersecretion (NNH = 17.9) and clinically significant (≥7%) weight gain (NNH = 28). The weight gain appeared to increase with aripiprazole dose (aripiprazole, 10 mg 4.0%, 30 mg 12.3%, placebo 4.6%). Overall data suggests that aripiprazole is associated with a greater risk for akathisia than the other SGAs and lower levels of weight gain NNH (risperidone 11.1, olanzapine 2.5, quetiapine 8.2, aripiprazole 28.0, ziprasidone 33.3) and a negligible risk of hyperprolactinaemia.

I am not aware of any data relating to quality of life or other patient reported outcomes.

For reasons described above it should be clear that this guidance relates only to those meeting criteria for bipolar 1.

There are always important differences between clinical trials routine clinical practice. As noted above any trial that includes individuals with bipolar 2 or NOS or a high proportion of subjects with comorbid ADHD is likely to reflect a very different population to that seen in clinical practice in the UK. However the main trials referred to above relate to bipolar 1 and are likely to reflect reasonably well the type of patient seen in the UK. However as with all registration trials the subjects are relatively “clean with respect comorbidity.

Clinicians in the UK do not always use standardised rating scales to monitor outcome. This should have ever be encouraged and the Young Mania Rating Scale which is used extensively in clinical trials would be an appropriate instrument for UK clinical practice.

Any additional sources of evidence

The Royal College of Psychiatrists is concerned that the timing of this technology appraisal may have an unintended impact on the review of the NICE bipolar guidelines. This occurred with the technology appraisal for aripiprazole in adolescents with schizophrenia whereby the the NICE guideline on Psychosis and Schizophrenia in children had to incorporate the Single Technology appraisal of Aripiprazole in the treatment of 15-17 year olds with schizophrenia. This caused significant problems as the STA recommended, on the basis of a rather poor evidence base, the use of Risperidone as the first treatment. We are concerned that

poor co-ordination between the technology appraisal for this drug in bipolar disorder in 15 – 17 year olds will create problems for the forthcoming bipolar guideline update

Implementation issues
NHS staff would need some extra education and training?

Equality
It is likely that those with significant intellectual disability would not be covered by this guidance as the evidence base does not extend to this population.