COVENTRY AND WARWICKSHIRE PARTNERSHIP TRUST
Evidence for the unlicensed use of atypical antipsychotics (aAPD) in the treatment of
Generalised Anxiety Disorder (GAD)

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Review Date: May 2013

1 Background

• **Pharmacological approaches** to treat GAD (defined by DSMIV as a chronic anxiety disorder of at least 6 months duration): NICE recommends an SSRI (selective serotonin reuptake inhibitor) first line; second line another SSRI or SNRI (serotonin and noradrenaline reuptake inhibitor); to consider pregabalin if person cannot tolerate an SSRI or SNRI.
• **Mode of action of aAPDs in the treatment of GAD:** thought to be due to antagonism at 5HT2A receptors and/or partial agonism at 5HT1A receptors/ antihistamine effect.

1.1 **Evidence for the use of atypical antipsychotics:**
In the development of their anxiety guidelines, the NICE Guideline Development Committee reviewed the evidence for use of APDs. They reviewed data for olanzapine, risperidone and ziprasidone. Quetiapine was excluded, as there were plans for it to be considered separately (NB the licence application for this has now been withdrawn). The Committee concluded that the limited benefits did not appear to justify the harms caused by augmentation (discontinuation of therapy due to adverse effects). They recommended that augmentation with APDs should only be provided in specialist settings, using specialist expertise; the use of an atypical antipsychotic was not recommended for the management of GAD in primary care.
A review of the use of aAPDs as adjunctive agents for Treatment Resistant GAD identified 12 clinical trials. The aAPD in these studies were aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone. The review stated that many of the studies were open label, and/or included small numbers of patients. The authors recommended that more rigorous studies are required, and that the use of aAPDs should only be considered for those in whom other treatment strategies have failed.
Astra Zeneca have withdrawn a licensing application for quetiapine in the treatment of GAD.
The Psychotropic Drug Directory states that aAPD have little proven efficacy in GAD, and have marked side effects.

1.2 **Dose:** should be individualised with close monitoring of efficacy and adverse effects.

1.3 **Side effects:** include weight gain, hyperglycaemia, dyslipidaemia, dry mouth, risk of serotonin syndrome.

1.4 **Prescribers** considering prescribing atypical antipsychotics in the treatment of GAD should follow the Medicines Policy Guidance for prescribing unlicensed medicines and ensure that they:
• Exclude licensed alternatives – Note: a number of the older typical antipsychotics are licensed for use in anxiety but not specifically for GAD. E.g. Flupentixol as Fluanxol is licensed for the symptomatic treatment of depression (with or without anxiety). Chlorpromazine is licensed for as an adjunct in the short-term management of anxiety psychomotor agitation excitement, violent or dangerously impulsive behaviour.
• Ensure familiarity with the evidence base
• Consider the contraindications and precautions for use (as listed in the SPC)
• Consider and document the potential risks and benefits – sharing the risk assessment with the patient and carers if applicable.
• Close monitoring for efficacy and side-effects

**NB** The Drugs and Therapeutics Committee recommend that an atypical antipsychotic is only used if other agents with more evidence of efficacy in the treatment of GAD have been trialled and found ineffective. The patient should be monitored closely for evidence of efficacy and/or the emergence of side effects.

2 References:

1 NICE anxiety: full guidance. CG113 2011
2 Lorenz RA, Jackson CW, Saitz DO. Adjunctive use of atypical antipsychotics for treatment-resistant generalized anxiety disorder. Pharmacotherapy. 2010;30(9):942-951
3 http://guidance.nice.org.uk/TA/Wave23/29
4 S Bazire. Psychotropic Drug Directory 2010 p 24