

## Prescribing psychotropic medication during the perinatal period: an overview of the 2017 British Association for Psychopharmacology consensus guidance

### Abstract:

The use of psychotropic medication in pregnant and breastfeeding women is an area of great challenge for both women with mental health problems and clinicians. There are many uncertainties regarding risks of untreated illness on mother, fetus or infant as well as concerns over potential risks to the fetus or infant associated with use of psychotropic medications during pregnancy or breastfeeding. The purpose of the guidelines is to provide advice regarding making decisions around treating mental illness in the perinatal period. This article provides a summary and explanation of the consensus guidance.

### Keywords

Antidepressants, antipsychotics, anxiolytics, birth defects, breastfeeding, child development, conception, fertility, hypnotics, mood stabilisers, neonatal problems, postpartum, pregnancy, pregnancy outcome, psychiatric illness, psychotropics, teratogenicity

### Introduction

**Prescribing in the perinatal period is challenging for both patient and doctor. Risks in utero, or via breast milk exposure to medication to the fetus and infant need to be balanced against the risks of untreated illness to both mother and child.**

### *Background of the guidelines*

The British Association of Psychopharmacology (BAP) produces evidence based guidelines for use of medication in patients with psychiatric disorders. Given the extent of great uncertainty that exist in prescribing in the perinatal period, this is an area in which clinicians are perhaps particularly dependent on guidelines. The guideline's purpose is to give pragmatic guidance. It was created following a consensus meeting with input from experts in the field of perinatal psychiatry, psychopharmacology, teratology, infant and child development and service user representatives. As BAP were creating this guideline, the National Institute for Health and Clinical Excellence (NICE) were publishing revised perinatal guidelines CG192 (NICE, 2015). Recognising that conflicting guidelines would be detrimental for clinicians and patients, BAP paused their work awaiting publication of NICE CG192. After reviewing the new NICE guideline BAP continued to work on this guideline with the aim of complementing CG192 and providing practical clinical recommendations. NICE CG192 clearly recommends shared decision making regarding options to treat or prevent mental illness and suggests that these discussions cover potential benefits of treatment, possible consequences of no treatment, possible harms from treatment and possible effects of changing or stopping treatment (NICE, 2015).

### *Overview of the guidelines*

The BAP 2017 perinatal guidelines consists of four broad parts which seek to address the areas of discussion recommended by NICE CG192; risks of untreated illness, generic guidance on using medication in the perinatal period, benefits and harms associated with individual treatments and recommendations for the pharmacological management of specific disorders. The scope of each of the four parts is described in Table 1. The term 'perinatal' in these guidelines is used to include the period from preconception, through pregnancy and to the end of the first year postpartum. (McAllister-Williams et al, 2017).

**Table 1. The four main areas of the BAP 2017 Guidance and the scope of each section.**

Area of guidance	Scope
1. Risks of untreated illness	Describes the risk to mothers and their children of psychiatric illness and symptoms particularly when untreated
2. Using medication in the perinatal period	Discusses general principles of using medication in the perinatal period
3. Benefits and harms associated with individual medication and treatments	Reviews the risks associated with specific psychotropic medications and treatments.  Includes antidepressants, anxiolytics, antipsychotics, lithium, anticonvulsant mood stabilisers, attention deficit hyperactivity disorder (ADHD) medications, substance misuse medications and neuromodulatory treatments.
4. Recommendations for the pharmacological management of specific disorders	Provides guidance on the management of psychiatric disorders in the perinatal period.  Includes depression, anxiety disorders, bipolar disorder, psychosis, eating disorders, ADHD, substance misuse, personality disorders and acute behavioural disturbance,

A summary of each section of the guidance is provided below.

## Overview of part 1: Risks of untreated illness

### *General risks of untreated illness*

The risks of untreated illness in the perinatal period is underlined by the results of the Confidential Enquiry into maternal deaths. Maternal suicide remains the leading cause of direct deaths in the first year postpartum (Knight et al, 2017).

Women with untreated mental illness in pregnancy are less likely to fully engage in antenatal care (Kim et al, 2006). They are also more likely to misuse nicotine, alcohol and other substances which have their own negative impacts on pregnancy outcomes (Shah and Howard, 2006; Zhu and Valbo 2002; Zuckermann et al 1989). Furthermore there is an impact of untreated maternal mental illness on the rest of her family, including relationships with her partner and any other children. Maternal depression is known to be a risk factor for postnatal paternal depression (Bradley and Slade, 2011; Burke, 2003).

When considering the risks of untreated illness, it needs to be noted that much of the evidence available includes studies of women with symptoms of specific conditions and not necessarily meeting defined diagnostic criteria of particular disorders. Furthermore, effects on offspring may be confounded by shared genetics rather than a pure effect of maternal illness in the perinatal period (McAllister-Williams et al, 2017).

### *Risks related to specific untreated disorders*

Risks related to specific untreated disorders are described in Table 2

#### **Table 2: Risks related to specific untreated disorders.**

Untreated disorder	Associated risks
Untreated depression and untreated anxiety	<p>Preterm delivery and low birth weight (Alder et al, 2007; Grote et al, 2010)</p> <p>Risk of low birth weight increases with severity of depression (Steer et al, 1992)</p> <p>Conduct disorder and ADHD symptoms in offspring (Glover, 2014)</p> <p>Poor engagement and bonding with infant leading to poor infant learning and cognitive development (Sutton et al, 2012)</p>
Untreated bipolar disorder	<p>High risk of relapse post partum</p> <p>Very high risk of puerperal psychosis (Wesseloo et al, 2016)</p>
Untreated schizophrenia	<p>Acute psychosis in first year postnatally (Munsk-Olsen et al 2009)</p> <p>Adverse obstetric and neonatal outcomes (Bennedsen et al 1999, 2001; Cannon et al, 2002; Dalman et al, 1999; Howard et al, 2003; Jablensky et al, 2005; Vigod et al, 2014)</p>
Untreated eating disorders	<p>Increased risk of perinatal depression and anxiety (Easter et al, 2015; Micali et al, 2011)</p> <p>In Anorexia Nervosa: low birth weight (Solmi et al, 2014) and small for gestational age babies (Micali et al, 2016)</p> <p>In Bulimia Nervosa/Binge eating disorder: large for gestational age babies (Linna et al, 2014)</p>
Untreated substance misuse	<p>Cannabis is associated with low birthweight and preterm labour (Metz and Stickrath, 2015)</p> <p>Opioids are associated with increased risk of fetal growth retardation, placental abruption, fetal death and preterm delivery (Center for Substance Abuse Treatment, 2008)</p> <p>Stimulants are associated with preterm labour, congenital abnormalities, intrauterine growth retardation (IUGR), placental abruption, low birth weight, neonatal death and SIDS (Debooy et al, 1993, Fox, 1994; Ryan et al 1987). Also maternal complications of pre-eclampsia-like-syndrome, acute pulmonary oedema, seizures, cardiac arrhythmia and sudden death (Fox 1994; Ryan et al, 1987). Use prior to delivery related to neonatal withdrawal (Chomchai et al, 2004, Smith et al, 2003)</p>

### [Overview of part 2: Use of medications in the perinatal period](#)

Whilst it may be tempting for clinicians to jump to section 4 to ascertain how to treat specific disorders in the perinatal period, it is paramount that section 2 is given careful consideration. In this section general principles of using medication in the perinatal period are discussed. The guidelines aim to convey that there is not a set recipe to follow when treating psychiatric disorders in the perinatal period, more a way of thinking that needs to be adopted. The necessity of this approach owes to the lack of evidence and data in many areas of the field. As such, risks are extremely hard to quantify. RCTs exploring use of psychotropic medication in pregnancy and breastfeeding are lacking due to

difficulties with safely including this patient group. Much information regarding risks of using psychotropic medication in the perinatal period is from population data and is retrospective and therefore has associated biases. The confounding factors in this type of data include concomitant use of alcohol, substances and smoking as well as the underlying indication for the psychotropic medication. For example, if adverse effects are reported for an antidepressant, it is difficult to establish if the effects are due to the drug itself or related to the underlying depression for which the drug was used.

Furthermore, in the data available there tends to be an over-reporting of abnormalities compared to normal outcomes. There is also the problem that minor and perhaps clinically insignificant abnormalities are reported along with serious malformations.

### *Key principles of prescribing in the perinatal period*

There are several key principles of prescribing in the perinatal period. These apply to all childbearing stages.

#### **1. Understanding a woman's individual illness**

It is important to understand the nature, severity and course of the illness for the individual woman. Clinicians should be asking themselves "what is this illness like for this individual woman?" Box 1 highlights important information to consider to inform management choices.

- How frequently does the illness relapse and what happens when it does?
- What are the triggers for relapse?
- What are the risks when unwell?
- How helpful have medications been at treating illness and preventing relapse?
- How long has the illness been in remission both on and off medication?
- What has been the time to relapse on discontinuing medication?
- What has been the time to recovery on restarting medication?
- Is there a personal history of perinatal illness?
- Is there a family history of severe perinatal illness?

Box 1: Information to gather from an individual woman's history to guide management options.

#### **2. Discussions with the woman (and partner)**

It is important to check if the woman and her family have been sufficiently educated about her illness, including if and how childbearing may affect its course. It is also important to assess her (and potentially her partner's) attitude to balancing risk of recurrence of mental illness against the safety of medication.

#### **3. Consideration of non-drug alternatives**

On weighing up the above factors then non drug options may be preferable.

#### **4. Rationalising existing treatment**

If a woman is on several different medications, it is advised to take a careful history of each drug and its effectiveness. Try to prescribe as few drugs as possible at the lowest effective doses as determined in the individual patient. Such doses may vary between women and it is important that individuals are not prescribed sub-therapeutic doses since this exposes the fetus to potential risks without conferring any therapeutic benefit to the woman. It may be more appropriate to use a drug of known

efficacy in a particular woman rather than a drug that is of unknown efficacy in her illness but carries a lower pregnancy risk.

#### **5. Provision of care and collaboration between services**

Due to the high risks associated with recurrence in the perinatal period women with a history of severe mental illness should be under the care of mental health services; perinatal mental health services where possible. Given that women potentially access several services in the perinatal period, including primary care, maternity care, health visitors, neonatology and Children's Services there needs to be close collaboration between all those involved in the care around her. A perinatal mental health care plan should be drawn up and shared with relevant professionals. This should include her care needs, ongoing pharmacological and psychosocial interventions, information about possible risks to the newborn, plans regarding breastfeeding and what the medication plans are for this phase. Each professional's roles in monitoring, providing intervention or coordinating care should be detailed. There should also be a plan that allows other professionals to identify when psychiatric review might be needed and how this can be accessed.

#### *Considerations specifically for the preconception period*

There should be discussions with all women of childbearing potential who are taking psychotropic medication or who have a history of severe mental illness about the implications of pregnancy and childbirth on both her mental health and associated risks of any medication she is taking. Some medications are associated with very early teratogenicity, for example valproate or carbamazepine. With such medications adverse effects may have occurred before confirmation of pregnancy. There should be discussions around contraception in such cases. In the case of valproate Medicines and Healthcare products Regulatory Agency (MHRA) Valproate Pregnancy Prevention Programme should be followed which includes ensuring highly effective contraception is in place. Highly effective contraceptive options are those with less than 1% failure rate with typical use. Highly effective contraceptive methods include long acting reversible contraceptives, copper intrauterine device, levonorgestrel intrauterine system, progestogen only implant (IMP) and female sterilisation (MHRA, 2018).

Options available to women of childbearing potential or specifically planning a pregnancy could be to continue with their current medication regime, switch to a regime with fewer fetal or maternal adverse effects or discontinue medication completely. Any discontinuation of medication should be done slowly to lessen the risk of relapse and allow monitoring of the woman's mental state. Women should be advised as to how long to continue contraception following discontinuation of medications based on half-lives and risks of teratogenicity.

#### *Specific considerations during pregnancy*

Women with a history of severe mental illness should be managed as a high risk pregnancy. Other modifiable risk factors for example, substance use, smoking, alcohol and weight management should be addressed. It is important to remember that smoking is the leading preventable cause of fetal morbidity and mortality in the UK (McAllister-Williams et al, 2017).

The risks and benefits of continuing current medication regimes, changing or discontinuing should be discussed with the woman, taking into account the individual factors listed in Box 1. Unless there is a good reason, changes in medication should be avoided in pregnancy. If a woman is taking a medication known to carry a significant risk of fetal abnormalities then she should be offered early

detailed ultrasound scanning. Women taking second generation antipsychotic should be monitored for gestational diabetes and offered a glucose tolerance test (NICE, 2015).

The risk of neonatal adaptation syndromes needs to be considered in the later stages of pregnancy. Most neonatal adaptation syndromes are mild and transient, but may be more pronounced in an intrauterine growth retarded (IUGR) or sick baby. Consideration can be given to lowering the dose of medications close to the due date to reduce the risk of neonatal withdrawal, however given that delivery dates are not certain for many women this strategy risks a period of under-treatment for the mother and therefore potentially increases the risk of relapse.

#### *Specific intrapartum considerations*

It is recommended that women with severe mental illness should deliver in hospital. The maternity team in hospital need to be aware of any medication issues for this period, for example, stopping lithium at the onset of labour to avoid maternal and neonatal toxicity (Newport 2005) or a woman may need to start an antipsychotic immediately following delivery if she is at risk of post-partum psychosis.

#### *Specific considerations postnatally and for breastfeeding*

The WHO recommends that 'infants should be exclusively breastfed for the first 6 months of life to achieve optimal growth, development and health' (WHO 2003). Care should be taken when prescribing psychotropics to avoid over sedation, which may hinder both breastfeeding and ability to provide baby care. There is very limited evidence regarding longer term outcomes in infants breastfed by mothers taking psychotropic medication. There is little evidence to support timing of breastfeeding around medication doses, and indeed this may hinder breastfeeding.

Similarly to pregnancy, an individual woman's response to previous medication is the best guide for future treatment choices. Where a mother is taking psychotropic medications, breastfed infants should be monitored for adverse effects including sedation or poor feeding.

There needs to be extra caution applied to prescribing in breastfeeding women where the infant is sick, premature or the mother is taking multiple drugs.

### *Overview of parts 3 and 4: Benefits and harms associated with individual medications and management of specific conditions*

Medication classes and specific drugs and treatments are considered in section 3. They include antidepressants, anxiolytics, antipsychotics, lithium, anticonvulsant mood stabilisers, attention deficit hyperactivity disorder (ADHD) medications, substance misuse medications, neuromodulatory treatments. For the category of drug each stage of the perinatal period is considered. The guidance reviews effects on fertility, pregnancy and pregnancy outcomes.

Section 4 of the guideline discusses management of specific conditions in the perinatal period. When managing any condition perinatally it is important to refer back to the generic principles set out in section 2, 'using medication in the perinatal period'.

The sections of the guideline should be used in conjunction with each other to help clinicians develop a management plan for individual women with individual conditions. We illustrate this with regard to the management of depression in the perinatal period.

#### *An example: management of depression in the perinatal period*

This worked example is divided into the three phases of pre conception, antenatal and postnatal care and illustrated in Table 3.

**Table 3: The management of depression in the perinatal period**

Perinatal Phase	How to navigate the guidance
Preconception	<p>Review section 2 'recommended principles for prescribing to women in the perinatal period' to inform individualised plan regarding commencing or continuing antidepressant treatment</p> <p>Review section 3 'antidepressants' in 'benefits and harm associated with individual medications' to guide choices</p> <p>No current antidepressants are absolutely contraindicated in pregnancy. SSRIs have the largest evidence base for reproductive safety and are often first line treatments in antidepressant naïve women. (Cleare et al, 2015; NICE, 2009).</p> <p>If a woman has had antidepressants before, be guided by principles in section 2 'recommended principles of prescribing to women in the perinatal period'</p>
Antenatal	<p>All pre conception recommendations apply</p> <p>Generally do not suddenly discontinue medication due to risk of relapse and discontinuation syndrome</p> <p>Late in pregnancy, risk/benefit of PPHN needs to be considered</p> <p>Take into account intentions for breastfeeding thus avoiding the need to alter treatment postpartum</p>
Postnatal	<p>Antenatal depression leads to an increased risk of postnatal depression. Therefore if antidepressant treatment required in pregnancy likely to be of benefit postpartum.</p> <p>When a woman chooses to breastfeed, review 'recommended principles of prescribing to women in the perinatal period: postnatally and breastfeeding'</p>

### Limitations of the guideline

Data relevant to both this guideline and prescribing in the perinatal period in general are emerging constantly. Therefore it is recommended that prescribers keep up to date with new information. An example is that since this guideline was finalised there has been a further observational study published on the rates of major congenital malformations associated with anticonvulsants (Weston et al. 2016) and a case-controlled study of the risk of malformations with in utero exposure to metformin was generally reassuring (Given et al. 2018) – an important observation given the recommended use of metformin for antipsychotic induced weight gain (Cooper et al. 2016). UKTIS (<http://www.uktis.org>) provides information on fetal risk. Any modifications required to this guideline prior to its update and republication will be posted at <http://www.bap.org.uk/perinatalupdates>. It is recommended that these BAP consensus guidelines are used in conjunction with the NICE perinatal guidelines (Nice 2015).

## Conclusions

When managing any psychiatric disorder in the perinatal period, taking into account the woman's individual illness history and response to treatment is paramount. This information can then be used to tailor discussions around risks and benefits to her particular circumstances. Whilst acknowledging that data on safety are limited, the risks of untreated illnesses must not be ignored. Shared decision making with the woman is best practice and it is important to ensure that all relevant members of the team across different services involved in the woman's care are aware of treatment plans and their role in management or coordination.

## Key messages

- **Data regarding risks and benefits of psychotropic medications in the perinatal period have many weaknesses, in particular the multiple confounding factors. This makes definitive statements about risks and benefits impossible in many cases.**
- **Untreated psychiatric illness in the perinatal period carries risks to the mother, fetus and infant.**
- **When considering management plans there are no set ways to treat specific illnesses. Individual decisions should be based on the patient's own illness, past treatment history and personal preferences.**
- **Valproate is the only psychotropic contraindicated in women of childbearing potential when used for psychiatric indications, although there can be very rare exceptions.**

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