An overview of the new BAP perinatal guidelines.

Last year the British Association for Psychopharmacology (BAP) published its guidance on perinatal care. In his presentation, Professor Hamish McAlister-Williams, from Newcastle University and co-author of the new BAP guidance, summarised the new recommendations and the emphasis on individualised care and patient history.

The guidelines are divided into four parts: the risks of untreated illness, guidance on using medication in the perinatal period, the benefits and harms associated with individual treatments and recommendations for the pharmacological treatment of specific disorders. “They certainly should not be diktats though, and following guidelines blindly can often do more harm than good, particularly in perinatal care”, warned Prof. McAlister-Williams.

Anxiety and depression in the mother during pregnancy is known to be associated with low birth weight and preterm delivery, and long term behavioural and mental health problems in the offspring. Less evidence is available on the impact of schizophrenia and bipolar disorder in pregnancy, though bipolar disorder is the most significant risk factor for postpartum depression or an episode of psychosis: “increased from a risk factor of maybe as low as 1 in 1000 to 1 in 4 – a massive 250-fold increase”, said Prof. McAlister-Williams. Schizophrenia is associated with a range of obstetric and neonatal outcomes, such as babies being born small for gestational age.

The section on using medication in the perinatal period, “is the most important part of the guidance”, said Prof. McAlister-Williams. “And the most important thing of all is to make decisions individualised to that specific patient based on their own illness and past treatment history. This requires a much closer collaboration between primary and secondary care, and obstetric services, with mental health services”.

When prescribing an antidepressant in pregnancy, the “risks of the illness seems to outweigh the risks of the treatment”, said Prof. McAlister-Williams. Evidence shows that children of women treated for depression in pregnancy tend to do better than those in cases when the mother was not treated for their depression, especially in cases of severe depression. An SSRI can increase the risk of postpartum hemorrhage, but the absolute risk remains low; and in patients that become severely depressed during pregnancy, but that have not used an antidepressant before, the BAP recommendation is to start them on sertraline. “However, we are not recommending that every woman who is pregnant and needs an antidepressant should go onto sertraline! Quite the converse, we recommend that the patient history should be the most factor important in choice of medication, so previous response to previous episodes”, said Prof. McAlister-Williams.

Antipsychotic medication is associated with a possible risk of gestational diabetes in the mother and neuro-motor delay in the infant when they reach 5-10 years of age. “Again, the best indicator of which drug to use is the patient’s past history, and we do not recommend switching medication because the risk of relapse is high”, said Prof. McAlister-Williams. If the patient continues with their medication during and post-pregnancy then close monitoring of the baby is necessary once they are born. Breast-feeding is a contraindication in babies whose mothers are being treated with clozapine because of the potential risk of granulocytosis.

Similarly, in patients using lithium during and post-pregnancy the guidelines suggest avoiding breast-feeding as there is a potential risk to the infant’s kidney and thyroid.
function. However, “the magnitude of risk quoted in many of the textbooks is way higher than current evidence would actually suggest”, said Prof. McAlister-Williams. Also, sudden discontinuation of lithium is associated with a significantly high risk of mania in the mother. If it is to be discontinued then slowly taper lithium levels over a four-week period.

Valproate is one of the few places the BAP guidelines make a very specific recommendation - that it should not be used in pregnant women or any woman of childbearing age due to associated risks.\textsuperscript{1} For other anti-epileptic and anti-epileptic mood stabilisers, carbamazepine can increase the risk of congenital malformations, but as lamotrigine is no longer strongly associated with cleft-palate or cleft-lip “it is the one of these three that we would feel more relaxed about prescribing during pregnancy”, said Prof. McAlister-Williams.

“With the exception of valproate, there are very few absolutes in the guidance but if any medication has been stopped then consider restarting it IMMEDIATELY post-natally, because the relapse risk is highest in the first week, indeed in the first 24 hours”, concluded Prof. McAlister-Williams. “I would also really emphasise the importance on the sections for substance misuse, as we know there are high rates of substance misuse, particularly in patients with mental health problems that are pregnant”.

**Inflammation and mental health: a revolution in psychiatry**

Increasing recognition of the role of inflammation in mental health could change the way certain conditions are treated in the future. In his presentation, Dr Carmine Pariante of King’s College, London, outlined current research showing that depression could be considered as an autoimmune disease.

“Through this revolution we can perhaps create new biomarkers and new treatments that would be especially relevant for patients with depression that are not currently responding to medication”, said Dr Pariante. “For many of you, it will be accepted knowledge that the immune system is not just some kind of army that keeps viruses and bacteria at a distance and actually we can understand it as a complex regulatory system that interacts continually with the brain”.

In evolutionary terms the connection between the immune system and brain is out-of-sync with the stresses of modern life. “Until relatively recently, most stressors would be a stressor that creates physical damage. It would not be about poverty, unemployment or relationship difficulties – it would be the stress induced by a predator”, said Dr. Pariante. “Until the discovery of antibiotics, infection was the reason why most people died - so in a way it makes perfect sense that in a condition of stress the immune system gets activated. It wants to protect the body from a very likely infection from fighting with predators.”

It is now recognised that severely depressed patients often have higher than average levels of cortisol in their system. Cortisol is a glucocorticoid hormone that is an immunosuppressant, preventing the release of substances involved in inflammation. Interestingly, a 2008 study\textsuperscript{2} showed that depressed patients had significantly higher levels of cortisol AND interleukin-6 (IL-6), which is a pro-inflammatory cytokine released in autoimmune and infection responses, than was seen in the control group. “This is an interesting biological conundrum because cortisol is meant to be immunosuppressant”, said Dr. Pariante. “So how do you have a coexistence of high inflammation and a high level of cortisol in the same patient?”

The research found that in depressed patients there was a disruption in communication between the circulating cortisol levels and immune cells in the blood. “So, in other words, there is a mechanistic block, so that even if cortisol levels are elevated it cannot exert the anti-inflammatory action on the immune cells”, said Dr. Pariante. This creates an escalating process where more cortisol is produced to tackle the inflammation, yet inflammation is not reduced.

To explain this mechanism, a 2012 study\textsuperscript{3} measured how many receptors for cortisol existed in the immune cells in depressed patients, with results showing significantly less cortisol receptors in depressed patients than in the control group. Surprisingly, the study also showed an excess of the FKBP-5 protein in depressed patients, which binds to the receptor for cortisol, blocking it and keeping it an unresponsive state, “so you have double hit”, said Dr. Pariante. “There are less receptors for cortisol and the little that is there is kept inactive by an excess of FKBP-5. That is the signature why patients with depression respond less to cortisol and why their immune cells are activated”.

So what causes this? In some patients their genetic build-up predisposes their immune system to be hyperreactive. In others it can be caused by a neurodevelopmental trajectory, stemming from childhood trauma, that primes an individual’s immune system to be hyperreactive and leads to depression in adulthood. A 2008 study\textsuperscript{4} compared numerous biomarkers between participants that were either healthy, suffered from depression, suffered maltreatment without depression, or suffered maltreatment and depression. In patients with depression there was a 1.15 increase in immune system activation compared to healthy individuals, but this doubled to 3.0 in patients
that had been maltreated but did not have depression.

“These results confirm the notion that being maltreated activates the immune system”, said Dr. Pariante. “Arguably this then creates a trajectory for depression as the immune system is already hyperreactive… and this group will probably become depressed in later life due to these biological changes”. In evidence, the study showed patients with depression and a history of maltreatment had the highest levels of inflammation of any group.4

In starting this biological trajectory, “how early is early?”, asked Dr Pariante. “Even exposure to stress in-utero is enough to increase a trajectory of immune activation”, with a longitudinal study showing that offspring exposed to depression in pregnancy were nearly four times more likely to have increased levels (>3 mg/L) of serum C-reactive protein - a protein synthesised by the liver in response to IL-6 - than offspring not exposed to depression during pregnancy.5

Understanding these biomarkers in the blood “brings personalised medicine into psychiatry for the first time”, said Dr. Pariante. Using a simple blood test in clinic will discern which depressed patients will respond well to antidepressants (patients with lower levels of cytokines and IL-6), or patients that will not (those with high cytokine levels and inflammation) – “so that we can escalate treatment immediately and maybe combine anti-depressants with anti-inflammatories”.

“I am really convinced that this is the way forward for treating depressed patients that we cannot currently help today”, concluded Dr. Pariante. “The good news is that we have lots of anti-inflammatory treatments out there that could be used for depressed patients resistant to treatment”; however, more clinical studies need to be done. Dr Pariante is currently running a placebo-controlled clinical trial investigating the efficacy of minocycline in depressed patients with high levels of inflammation.

**Is schizophrenia a disorder of cellular cleanliness or homeostasis?**

“I am going to try and convince you that psychosis, or schizophrenia, has an element of pathology associated with disturbed protein regulation, and is probably an imbalance of homeostasis” stated Professor Ian Everall, from King’s College London, at the start of an engaging presentation on what the future holds for the treatment of schizophrenia.

Homeostasis is the cellular process all organisms use to self-regulate a stable internal environment, including in the brain. Neuronal homeostatic changes shown to be present in patients with schizophrenia include a decreased neuronal density and decreased neuronal size (especially in the hippocampus, cortex, substantia nigra and locus coeruleus). “The most robust anatomical findings that occur in the brain in schizophrenia are changes to synapses and dendrites, and all the markers you can think of show a reduction in dendritic and synaptic markers”, said Prof. Everall. When the innate immune system, gets activated it produces a series of pro-inflammatory cytokines (TNF-α and S100 proteins, for example). A 2006 study looked at an inflammatory S100 protein, called calprotectin, in the brain of schizophrenic patients and showed that it was significantly elevated. In a later 2012 microarray study it was demonstrated that in the brain of schizophrenic patients the S100A8 gene was the most altered gene in terms of high expression, with a five-fold increase in schizophrenic patients. “This shows there is an inflammatory component to psychosis and we are trying to still understand the contribution of that to the development of this clinical disorder”, said Prof. Everall.

“I think it is all about proteins”, said Prof. Everall. In a cell, the unfolded protein needs to be folded correctly to provide its function to the cell. If the protein is unfolded, or misfolded, then the ubiquitin proteasome system (UPS) needs to get rid of the protein to maintain proper cellular function – termed proteostasis. If this recognition doesn’t occur then the misfolded protein can form an aggregate that characterises neurological disorders such as Alzheimer’s and Parkinson’s Disease.

“This pathway goes wrong a lot in neurological problems but no one had really looked at it to see if it goes wrong in psychiatric conditions such as psychosis”, said Prof. Everall. In an unpublished study measuring ubiquitinated protein levels and ubiquitination activity in the brain and blood of patients with schizophrenia, “there was a decrease in the ubiquitination activity in the blood, but no change in the brain – so even though more proteins are being ubiquitinated and piling up, the actual ubiquitination activity is slowing down”, said Prof. Everall. “So, both the blood and the brain in schizophrenia is characterised by a build-up of the ubiquinated proteins, which the cell is not getting rid of”.

“There is growing evidence that this pathway may be going awry in schizophrenia”, said Prof. Everall. The activity of the UPS system is heavily reliant on the level of metals in the body, especially in iron. Iron activates Tyrosine hydroxylase, which is the enzyme that produces dopamine. In currently unpublished lab results, it has been shown that in the brain of schizophrenic patients there is an increase in the expression of iron and a decrease in α-synuclein, which
inhibits dopamine release. “So, the UPS system may be driven by changes in iron and we are now looking for this and its impact on dopamine synthesis”, concluded Prof. Everall.

The psychiatrist as expert witness
“Any contact with litigation can have devastating repercussions. Public humiliation is the least of it. The complete destruction of your reputation and in the worst cases the loss of your licence to practice”, warned Simon Di Rollo, Q.C., in a presentation advising psychiatrists what was expected of them as an expert witness.

Plenty of guidance exists on the responsibilities of psychiatrists that provide expert witness,8 basically though: “they provide an opinion, explain technical matters or terms, provide evidence of a fact, for example why someone with psychosis has behaved in a certain way, and take account of information stemming from the work of others”, said Mr. Di Rollo.

An expert witness is distinct from a professional witness (ie. the treating psychiatrist). The latter provides factual evidence on their patient(s), while an expert witness provides an opinion on the facts of a case that may not involve their patient(s). This distinction can become blurred, but the duty of an expert witness overrides any obligation to the person(s) they are asked to provide an opinion on.

“The important point to grasp as an expert is that you are now involved in a different relationship with the person that you are examining from the doctor-patient relationship”, said Mr. Di Rollo. “The Royal College say it is usually good practice for psychiatrists not to provide expert testimony about their patients... so you should look at the question of whether there is a conflict”.

There are clear rules on the opinions an expert witness can provide. “I want to emphasise that the decision is always for the court and not the opinion of an expert”, said Mr. Di Rollo. Expert evidence needs to be the independent product of the expert, and an expert witness needs to make it clear if they do not understand a question, or if it falls outside their experience. The four R’s should be used when preparing any material: retain, keep all material relating to the case; record, keep records of any work; reveal, provide all relevant material; and review, check work if new information presents itself.

“In relation to psychiatrists, it’s fair to say that they take a different view from lawyers”, said Mr. Di Rollo. “One way of summarising it is that psychiatrists look at mental disorder from a dimensional view, while lawyers take a legalistic or categorical approach, where it is either one thing or the other… so don’t be afraid to ask for clarification”.

There are also clear rules on when psychiatric expert evidence is required. In the 1975 trial R v Turner, when the defendant appealed on the basis that the court did not admit evidence of a psychiatrist to support their claim of provocation, it was ruled: “The fact that an expert witness has impressive scientific qualifications does not by that fact alone make his opinion on matters of human nature and behaviour within the limits of normality any more helpful than that of jurors themselves”.

“The decision is not as restrictive as it may seem”, said Mr. Di Rollo. Since then there have been some developments when psychiatric expert evidence has been used. For example, ‘battered women’ syndrome - when a woman does a serious injury to her partner though the event is not the subject of an immediate provocation - is a new area where expert evidence has been admitted. This is also true in examples of false confession evidence, when someone’s low IQ may mean that their testimony is invalid; and false memory, in cases that involve a diagnosable pathological liar.

“The legal system requests and demands the assistance of psychiatrists in a great many situations”, concluded Mr. Di Rollo. “And it is important that everyone involved in the administration of justice faces up to the challenges posed by obtaining the best evidence in skilled witnesses”.

References