

Pharmacology

Prescription opioids and neonatal abstinence syndrome

Neonatal abstinence syndrome (NAS) is a serious medical condition of the new-born occurring after in utero exposure to psychotropic medications. As yet, no figures exist to establish the risk of NAS among infants born to mothers using prescription opioid analgesia during pregnancy.

A recent population study gathered data from pregnant women across the USA who were using prescription opioid analgesia. The authors aimed to provide the risk estimates of NAS based on the duration and timing of opioid use.

In the cohort of 290 000 women, a total of 1705 cases of NAS were identified. This corresponded to an absolute risk of NAS of 5.9 per 1000 deliveries. Additional factors that increased the risk of NAS included long-term opioid use during pregnancy, alcohol or other drug misuse, and exposure to other psychotropic medications.

The use of prescription opioids during pregnancy is associated with a low absolute risk of NAS in the absence of additional risk factors.

Desai R, Huybrechts K, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *BMJ* 2015; 350: 2102.

The risk of lung disease with methotrexate

Methotrexate is frequently used for the treatment of many non-malignant inflammatory diseases. However, methotrexate has been implicated as a cause of serious lung disease.

Therefore, a recent study performed a meta-analysis to quantify the relative risk of pulmonary disease among patients with rheumatoid and psoriatic arthritis, psoriasis, and inflammatory bowel disease. A total of seven randomised trials were analysed to investigate respiratory adverse events of methotrexate compared with placebo or active comparator drug.

Together the studies comprised 1640 patients, reporting 946 patient-years of exposure. In total, 504 respiratory adverse events were documented among participants. Methotrexate was not associated with an increased risk of adverse events, respiratory infections, or non-infectious respiratory events. No pulmonary deaths were observed.

Patients with non-malignant inflammatory conditions treated with methotrexate had no increase of lung disease. Conway R, Low C, Coughlan R, et al. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ* 2015; 350: 1269.

Antipsychotic drug use in pregnancy

There has been a considerable rise in antipsychotic medication use in pregnancy over the past decade. Despite this dramatic rise, little is known about their use during pregnancy.

A population study aimed to evaluate maternal medical and perinatal outcomes associated with antipsychotic drug use in pregnancy. All 1021 participants had at least two consecutive prescriptions for an antipsychotic during pregnancy (specifically during the first or second trimester). Participants were matched 1:1 with non-user controls.

Data concerning the maternal medical outcomes demonstrated that antipsychotic drug use did not increase the risk of gestational diabetes, hypertensive disorders of pregnancy, or venous thrombo-embolism. The preterm birth rate was not increased among the antipsychotic group, and neither were the rates of low or high birthweight.

Antipsychotic drug use in pregnancy had minimal impact on important maternal medical and short-term perinatal outcomes.

Vigod S, Gomes T, Wilton A, et al. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. *BMJ* 2015; 350: 2298.

Global Health

Global access to surgical care

Previous estimates suggest that 2 billion people are unable to access surgical care. However, this estimate does not take into account capacity, safety, timeliness, accessibility, and affordability. Therefore, a commission aimed to re-estimate this figure by taking into account the aforementioned factors.

Using modelling data from 196 countries, the authors were able to estimate the proportion of the population in each country without access to surgical services.

At least 4.8 billion people do not have access to surgery. The proportion of the population without access varied widely by region. Over 95% of the population in south Asia, and much of sub-Saharan Africa, does not have access to care

compared with 5% of the population in Australasia, North America and Western Europe.

Most of the world's population does not have access to surgical care. The near absence of access in many countries represents a crisis.

Alkire B, Raykar N, Shrimel M, et al. Global access to surgical care: a modelling study. *Lancet Global Health* 2015; 3: 316–23.

Mass treatment for yaws

Yaws is a neglected tropical disease caused by *Treponema pallidum*. It causes primary and secondary cutaneous lesions and tertiary destructive lesions of the bone. The World Health Organization (WHO) has launched a new initiative to eradicate yaws by 2020. The proposed intervention involves mass treatment of the entire population with a single dose of oral azithromycin.

A recent study conducted on a Papua New Guinea island assessed the efficacy of this intervention. A total of 82.7% of the residents (n=13 302) received a single dose of azithromycin. The prevalence of active infectious yaws was significantly reduced from 2.4% to 0.3% one year after mass treatment. The prevalence of latent yaws among children aged 1–5 years was also significantly reduced from 18.3% to 6.5%. A total of 17% of participants reported mild medication side effects. No resistance to macrolides against *Treponema pallidum* was detected.

The prevalence of active and latent yaws infection fell substantially after mass treatment with azithromycin. Mitjà O, Houine W, Moses P, et al. Mass treatment with single-dose azithromycin for yaws. *NEJM* 2015; 372: 703–10.

Global epidemiology of yaws

Currently the knowledge regarding the geographic extent of yaws infections is incomplete. In order for the World Health Organization (WHO) strategy of yaws eradication to be successful, the scope of yaws infection needs to be determined. Therefore, a systemic review has been conducted to determine yaws epidemiology and to estimate at-risk populations in endemic countries.

Using databases, the authors identified studies that estimated the prevalence of yaws. The active disease estimates from the studies ranged from 0.31% to 14.5% in yaw-endemic areas, while the latent disease prevalence ranged from 2.4% to 31%. Of the 250 000 new cases reported to WHO during 2012–2013, 84% were from Papua New Guinea, Solomon Islands,

and Ghana. In Africa, 46.7 million people live in endemic areas, the majority of which reside in Ghana, Côte d'Ivoire, Cameroon, and the Republic of Congo.

Papua New Guinea, Solomon Islands, and Ghana should be the initial focus of efforts at implementing the WHO yaws eradication programme.

Mitjà O, Marks M, Konan D, et al. Global epidemiology of yaws: a systematic review. *Lancet Global Health* 2015; 3: 324–31.

Consequences of tobacco taxation

In 2010, tobacco use was estimated to be responsible for 5 million premature deaths. Tobacco taxation is extremely effective at reducing smoking and its negative impacts, while increasing government revenue. However, it has been criticised for disproportionately affecting poorer people.

In China, there are over 300 million male smokers. To assess the impacts of tobacco taxation on household health and finances, a cost-effective analysis was conducted across China.

Modelling analysis showed that a 50% increase in tobacco price through excise tax would lead to 231 million years of life gained over 50 years (a third of which would be gained by the poorest 20% of households). It would also increase tax revenues by US \$703 billion (the lowest income quintile would contribute 14%). Overall house expenditure on tobacco would fall by \$21 billion in the poorest 20% of households but increase tobacco expenditure in the remaining 80%.

Increased tobacco taxation can be a pro-poor policy whilst simultaneously providing substantial health and financial benefits.

Verguet S, Gauvreau C, Mishra S, et al. The consequences of tobacco tax on household health and finances in rich and poor smokers in China: an extended cost-effectiveness analysis. *Lancet Global Health* 2015; 3: 206–16.

Orthopaedics

Lumbar spine stenosis surgery: laminectomy vs microdecompression

Stenosis of the lumbar spine is characterised by back and leg pain numbness, and can also impair walking. Surgery is a successful form of management and can be performed using one of two different techniques. Traditionally, open laminectomy was the most common operation performed for the condition

but recently a shift towards minimally invasive surgical methods (such as microdecompression) has occurred.

To compare efficacy, a Norwegian observational study enrolled 855 patients undergoing either laminectomy or microdecompression surgery for lumbar spine stenosis. The outcomes compared included pain, ability to perform daily tasks, walking, sleep quality, and sexual function one year after surgery.

A total of 721 patients completed one year of follow-up. Favourable outcomes were observed at one year in both groups. However, results indicated that at one year, the effectiveness of microdecompression is equivalent to laminectomy in the treatment of stenosis of the lumbar spine. No difference was noted between the groups for the quality of life.

Both surgical methods are equally effective at one year.

Nerland U, Jakola A, Sölheim O, et al. Minimally invasive decompression versus open laminectomy for central stenosis of the lumbar spine: pragmatic comparative effectiveness study. *BMJ* 2015; 350: 1603.

Lumbosacral pain: steroid injections compared with gabapentin

The physical, socioeconomic, and psychological impact of low back pain is enormous. Epidural steroid injections are the most commonly performed procedure for the management of radicular pain. Nevertheless, research also indicates pharmacotherapy with gabapentinoids can be effective; however, little is known about their comparative efficacy.

A recent study compared the outcomes for both treatments among 145 participants with lumbosacral radicular pain. Each participant was given either epidural steroid injection plus placebo pills or sham injection plus gabapentin. The primary outcome measured average leg pain at one month.

Results showed a reduction in pain in both groups but there were no significant differences observed between the groups. However, those participants receiving steroid injections were temporarily more likely to experience a successful outcome than those receiving gabapentin.

Both steroid injections and gabapentin produced a modest reduction in pain. Any differences favouring steroid injections were modest and transient.

Cohen S, Hanling S, Bicket M, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. *BMJ* 2015; 350: 1748.

Cardiovascular

Diagnosing acute heart failure with natriuretic peptides

Making the correct diagnosis of acute heart failure in patients is challenging. Low levels of three types of natriuretic peptides (B type, NTproBNP, and MRproANP) can help exclude a diagnosis of chronic heart failure but levels of natriuretic peptides are only sporadically used for diagnosing acute heart failure.

Recently a meta-analysis compared the diagnostic accuracy of the three types of serum natriuretic peptides in patients presenting with acute heart failure.

At the lower recommended thresholds of 100 ng/L for B type NP and 300 ng/L for NTproBNP, the peptides had sensitivities of 0.95 and 0.99 and negative predictive values of 0.94 and 0.98 respectively. Using the recommended lower threshold of 120 pmol/L, MRproANP had a sensitivity in the range of 0.95–0.97 and a negative predictive value ranging from 0.90 to 0.97. Higher thresholds for the peptides resulted in declining sensitivity but the specificity remained variable.

B type, NTproBNP, and MRproANP natriuretic peptides have excellent ability to exclude heart failure.

Roberts E, Ludman A, Dworzynski K, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015; 350: 910.

Arteriovenous anastomosis for uncontrolled hypertension

Less than half of patients treated for hypertension achieve blood pressure control and most of these do not maintain long-term adherence. The creation of a central arteriovenous anastomosis results in an alteration of the mechanical properties of arteries that are, in turn, thought to reduce blood pressure.

To assess the efficacy of this intervention, a trial tested the impact of creating an iliac arteriovenous anastomosis (via catheterisation and a ROX coupler device) on systolic blood pressure in patients with uncontrolled hypertension.

A total of 195 patients were randomised to undergo implantation of an arteriovenous coupler device plus standard hypertensive treatment, or standard treatment alone. After 6 months, ambulatory blood pressure had reduced by 13.5 mmHg in the anastomosis group, compared with 0.5 mmHg in the control

group. Late venous stasis occurred in 29% of patients in the anastomosis group.

Arteriovenous anastomosis was associated with significantly reduced blood pressure and hypertensive complications. Lobo M, Sobotka P, Stanton A, et al. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet* 2015; 385: 1634–41.

Primary PCI with or without thrombectomy

Primary cutaneous intervention (PCI) is the most effective method of achieving reperfusion in patients with ST-elevation myocardial infarctions (STEMI) but can fail to restore microvascular flow due to distal embolisation. It has been postulated that thrombectomy before stent deployment may increase microvascular flow.

A recent trial with a cohort of 10732 patients diagnosed with STEMI were randomly assigned to undergo either PCI plus manual thrombectomy or PCI alone. The primary outcome measured death from cardiovascular causes, recurrent myocardial infection, cardiogenic shock or severe heart failure within 180 days.

The primary outcome occurred in 347 of 5033 patients (6.9%) in the thrombectomy group versus 351 (7.0%) in the PCI-alone group (insignificant hazard ratio, 0.99). Stroke within 30 days occurred in 0.7% of patients (n=33) in the thrombectomy group compared with 0.3% in the PCI-alone group (n=16).

Outcomes for patients with STEMI receiving PCI plus thrombectomy were not significantly better than those receiving PCI alone. However, the risk of stroke was greater.

Jolly S, Cairns J, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *NEJM* 2015; 372: 1389–98.

Rapid vitamin K antagonist reversal

Rapid reversal of vitamin K antagonist (VKA)-induced anticoagulation is often necessary for patients requiring urgent surgical or invasive procedures. In many countries, plasma is the most commonly used agent for rapid reversal however, four-factor prothrombin complex concentrate (4F-PCC) may be a suitable alternative.

To establish their comparative efficacy, a multicentre randomised trial assigned 181 patients requiring rapid

VKA reversal, in a 1:1 ratio to receive either plasma or 4F-PCC. The primary endpoints measured effective homeostasis and rapid INR (international normalised ratio) reduction (<1.3 at 30 minutes after infusion end).

Significantly more patients in the 4F-PCC group (90%), compared with 75% of the patients in the plasma group, achieved effective haemostasis. Further, rapid INR reduction was achieved in 55% of patients in the 4F-PCC group versus 10% in the plasma group.

4F-PCC is superior to plasma for rapid INR reversal and effective haemostasis. Goldstein J, Refaai M, Milling T, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015; 385: 2077–87.

Paediatrics

Antibiotic regimens for infants with serious bacterial infections

Many families from resource-poor settings with infants who are severely ill as a result of bacterial infections cannot accept hospital referral. In such cases guidelines suggest 7 days of injected procaine benzylpenicillin–gentamicin.

A sub-Saharan Africa trial assessed whether simplified antibiotic regimens may be as effective as standard antibiotic treatment for serious bacterial infections. A total of 3564 children were allocated to receive either injectable procaine benzylpenicillin–gentamicin for 7 days (reference group); injectable gentamicin and oral amoxicillin for 7 days (group B); injectable procaine benzylpenicillin–gentamicin for 2 days, then oral amoxicillin for 5 days (group C); or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D).

A total of 8% of children in the reference group failed treatment, compared with 6% in group B, 8% in group C, and 5% in group D. Fatality rates across the groups ranged from 1 to 2%.

The three simplified antibiotic regimens were as effective as injectable procaine benzylpenicillin–gentamicin.

Tshefu A, Lokangaka A, Ngaima S, et al. Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. *Lancet* 2015; 385: 1767–76.

Oral propranolol for infantile haemangioma

Infantile haemangiomas are the most

common soft-tissue tumours of childhood. Propranolol is first line therapy but current evidence assessing its efficacy is sparse.

In response, a randomised trial enrolled 460 infants with an infantile haemangioma. Each infant was then assigned to receive either placebo or one of four different oral propranolol regimens (1 or 3 mg of propranolol per kg per day for 3 or 6 months). The primary endpoint measured treatment success at 24 weeks.

The most effective propranolol regimen was 3 mg per day for 6 months. The frequency of successful treatment with this regimen was dramatically higher than with placebo treatment (60% vs 4%). A total of 88% of patients receiving the most effective propranolol regimen showed improvement by week 5 compared with 5% of patients receiving placebo. Propranolol-associated adverse events occurred infrequently.

Oral propranolol was effective at treating infantile haemangioma. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *NEJM* 2015; 372: 735–46.

Cerebral malaria: brain swelling and death

Case fatality among African children with cerebral malaria remains around 15–20%. Although the pathogenic processes behind these fatalities are unknown, it is thought that increased brain volume may lead to increased intracranial pressure.

Therefore, a magnetic resonance imaging (MRI) study was conducted among children diagnosed with cerebral malaria. To monitor brain volume, each participant had an MRI obtained on admission, and daily thereafter while the coma persisted.

Of the 168 children included in the study, 25 (15%) died, 21 of whom (84%) had evidence of severe brain swelling on admission. In contrast, severe brain swelling was only seen in 27% of survivors. Serial MRI scans showed decreasing brain volumes in the survivors who had had initial brain swelling.

Increased brain volume was seen in children who died from cerebral malaria, but was uncommon in those who survived the disease. This suggests that raised intracranial pressure may contribute to a fatal outcome.

Seydel K, Kampondeni S, Valim C, et al. Brain swelling and death in children with cerebral malaria. *NEJM* 2015; 372: 1126–37.

CPD Challenge

See page 38 to test yourself on this article

Infection

Kidney transplantation in HIV patients

The prevalence of chronic kidney disease among HIV-infected patients is now estimated to be over 20%. In 2008, South Africa starting performing kidney transplantation from deceased HIV-infected donors to HIV-infected patients requiring renal-replacement therapy. Now the 5-year follow-up for these patients has been reported.

A total of 27 transplantation patients were included in the study. The average follow-up of survivors was 2.4 years. Each recipient had a CD4 T-cell count of over 200mm³ and undetectable plasma HIV RNA level. All patients were receiving antiretroviral therapy.

The survival rate among patients was 84% at 1 year and 3 years and 74% at 5 years. The corresponding rates of graft survival were 93%, 84% and 84%. Rejection rates were 8% at 1 year and 22% at 3 years. HIV infection remained well controlled for the duration of follow-up.

Kidney transplantation appears to be an additional treatment option for HIV patients requiring renal-replacement therapy. Muller E, Barday Z, Mendelson M, and Kahn D. HIV-positive-to-HIV-positive kidney transplantation - results at 3 to 5 years. *NEJM* 2015; 372: 613-20.

Life expectancy of HIV-positive patients in Rwanda

Rwanda has achieved substantial progress in scaling up antiretroviral therapy (ART). To assess the impact of increased ART coverage among HIV-positive patients in Rwanda, researchers compared life-expectancy during two distinct periods of lower and higher ART coverage (1997-2007 and 2008-2011, respectively).

In total, 72 000 patients were included in the study, contributing over 200 000 person-years of follow-up. The crude mortality rate was 33.4 deaths per 1000 years. Life expectancy for the overall cohort was 25.6 additional years at 20 years of age and 23.3 additional years at 35 years of age. Life expectancy at 20 years of age in the period of 1997-2007 was 20.4 additional years; for the period of 2008-2011, life expectancy had increased to 25.6 additional years. Individuals enrolling with higher CD4 counts had highest life expectancies.

This study demonstrates the benefit of early enrolment of HIV-infected patients in care and initiation of ART.

Nsanzimana S, Remera E, Kanters S, et al. Life expectancy among HIV-positive patients in Rwanda: a retrospective observational cohort study. *Lancet Global Health* 2015; 3: 169-77.

Valganciclovir for congenital cytomegalovirus

Congenital cytomegalovirus (CMV) infection is a common cause of sensorineural hearing loss and mental retardation. Treatment for symptomatic congenital CMV involves intravenous ganciclovir for 6 weeks. However, whether the treatment produces long-term benefits remains unestablished.

A randomised trial assessed whether prolonging treatment to 6 months with oral valganciclovir improved hearing outcomes among 96 neonates diagnosed with symptomatic CMV. Participants were then given 6 weeks of ganciclovir followed by 6 months of either valganciclovir (6 month group) or placebo (6 week group).

Results showed that at 6 months, outcomes in hearing were similar between the two groups but by 12 months, participants in the 6 month group experienced a more favourable outcome. Further, those in the 6 month group scored significantly higher during neurodevelopmental assessments.

Treatment with valganciclovir for 6 months did not improve short-term outcomes but instead improved hearing and developmental outcomes in the long-term.

Kimberlin D, Jester P, Sánchez P, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *NEJM* 2015; 372: 933-43.

Obs & Gyn

International trends for caesarean section

The rates of caesarean section surgery are rising worldwide. However, the causes of this are controversial, especially in low- and middle-income countries.

A recent study aimed to analyse the determinants of the rising caesarean section rates. A total of 21 countries (from Africa, Asia, and Latin America) were surveyed and then stratified according to the Human Development Index (HDI) group (very high/high, medium, or low). The results from two surveys (conducted 2004-2008 and 2010-2011) were then used for analysis.

The overall caesarean section rate significantly increased between the two surveys, from 26.4% to 31.2%. Among

very high/high and low HDI countries, the use of obstetric interventions (induction, prelabour caesarean section) had also increased. The proportion of women who had previously undergone a caesarean section had risen in moderate or low HDI countries and are an increasingly important determinant of overall caesarean section rates.

Vogel J, Betrán A, Vindevooghel N, et al. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multicountry surveys. *Lancet Global Health* 2015; 3: 260-70.

Malaria prevention in pregnancy

In 2012, WHO guidance for intermittent preventative treatment of malaria during pregnancy (IPTp) changed to recommending monthly doses of sulfadoxine-pyrimethamine from the second trimester rather than two doses. However, the cost-effectiveness of this alteration has not been established.

In response, a modelling study has been performed to estimate the incremental cost-effectiveness of IPTp with three or more doses (IPTp-SP3+) compared with just two (IPTp-SP2).

The authors estimated that the disability-adjusted-life-years (DALY) lost for low birthweight, anaemia, and clinical malaria per 1000 women in the SP2 group was 555 compared with 442 in the SP3+ group. The delivery of IPTp-SP3+ to 1000 pregnant women averted 113.4 DALYs at an incremental cost of \$825.67 producing an incremental cost-effectiveness ratio (ICER) of \$7.28 per DALY averted. Further analyses demonstrated that, the ICER was \$4.0 per DALY averted for high risk of low birthweight.

This study suggests a monthly dose of IPTp-SP from the second trimester is cost-effective.

Fernandes S, Sicuri E, Kayentao K, et al. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for malaria during pregnancy in sub-Saharan Africa: a modelling study of meta-analysis and cost data. *Lancet Global Health* 2015; 3: 143-53.



Africa
HEALTH
CPD Challenge

See page 38 to test yourself on this article