CASE HISTORY

SPECIFICATION

This case history involved an adult female patient ZT, age 38 years who was pregnant (G7P2) with her third child and prescribed buprenorphine/naloxone for opioid dependence. My involvement with her care was between March 2015 and April 2016. There was a history of codeine dependence, principally over the counter ibuprofen-codeine. There was a past history of polysubstance use and psychiatric comorbidities. ZT had a complete miscarriage during March 2015 and during that period used ibuprofen-codeine, alcohol and nicotine. Her last child born on 15/10/2013 suffered severe Neonatal Abstinence Syndrome (NAS) and required a prolonged hospital admission of 8 weeks. During that pregnancy ZT was not prescribed opioid substitution therapy and used ibuprofen-codeine 30 tablets daily (384 mg codeine), alcohol 100-150 grams daily and nicotine daily.

ADDICTION MEDICINE CONTACT

ZT engaged with DASSA services from the age of 33 years.

Addiction Medicine was consulted during outpatient attendances and inpatient admissions for codeine and alcohol withdrawal on three occasions.

Addiction Medicine was involved with commencement and prescribing of buprenorphine/naloxone. Addiction Medicine Consultation Liaison Service (CLS) liaised with the hospital Antenatal clinic, Obstetric and Paediatric teams during pregnancy, labour and delivery, and during the postnatal period.

PRESENTATION AND SYMPTOMS - AUGUST 2015

ZT was a 38 year old mother of two children aged 7 and 19 months old. She lived with her children and partner in stable accommodation. At the time that pregnancy was confirmed ZT was approximately six weeks pregnant. This was a planned pregnancy. She was already prescribed 32mg buprenorphine/naloxone daily and was being dosed at a DASSA clinic with daily Breath Alcohol Concentration (BAC) prior to dosing. ZT reported use of ibuprofen-codeine co formulation (200mg-12.8mg) 6 tablets /day (76.8mg codeine) on 3 days per week and alcohol 40g daily on 3 days per week over the previous 4 weeks before pregnancy was confirmed. This was a reduction from past use of ibuprofen-codeine 30 to 40 tablets daily (384-512 mg codeine) and alcohol 100-150 grams daily. She had reduced her use following a miscarriage in March 2015. She reported no opioid or alcohol withdrawal on history and no withdrawal was evident on clinical examination consistent with the history. Her main focus at that time was to reduce her buprenorphine/naloxone dose due to her fear of NAS.

HISTORY

Drug and Alcohol History and Past Treatment.

OPIOID /CODEINE

October 2010 to 2011

ZT reported a six year history of codeine dependence. She commenced OTC codeine use for relief of generalised low back pain following a motor vehicle accident in

2010. She was driving under the influence of alcohol at the time. She reported enjoying the euphoric opioid effect and continued codeine use for relief of psychosocial stressors. She became dependent over a few months and reported use of 30-40 tablets ibuprofen-codeine daily (384-512mg codeine). ZT attended DASSA outpatients for counselling monthly. She decreased her use to 15 tabs daily (192 mg codeine) for a 2week period but resorted to previous use due to family and relationship stressors. The longest abstinence reported was 1week.

October 2011

FIRST admission for codeine and alcohol withdrawal.

Reported daily use of 30-60 tablets ibuprofen-codeine (384-768 mg codeine).

ZT described withdrawal symptoms of rhinorrhoea, backache, diaphoresis, agitation, headache and diarrhoea She reported daily alcohol use of 150 grams with variation in time of first alcohol drink dependent upon time of codeine use. She described alcohol use to alleviate codeine withdrawal during the day.

There was reported use of methamphetamine on one occasion in the previous 6 months, 1 point smoked 2 months previous.

Relapsed to codeine and alcohol post discharge.

January 2012 to April 2012

ZT reported ibuprofen-codeine use of 60 tablets daily (768mg codeine) on 20/28 days. Alcohol use 100-150grams daily.

April 2012

SECOND admission for codeine and alcohol withdrawal and relapsed post discharge.

April 2012 to June 2012

ZT completed a 5day buprenorphine/naloxone withdrawal as an outpatient on two occasions and achieved a maximum abstinence of 4 days duration.

Reported relapse due to psychosocial stressors.

January 2013

THIRD admission for codeine and alcohol withdrawal.

Discharged on naltrexone maintenance therapy 50 mg daily and ceased due to side effect of nausea. She relapsed after discharge.

ZT discussed her plans to conceive. She was advised of risks of substance use in pregnancy and offered another inpatient admission for withdrawal but declined.

<u>February 2013 to September 2014</u>

No contact with DASSA services

October 2013 -Second child born 15/10/2013 severe NAS.

July 2014 -Commenced on buprenorphine/naloxone by GP for 3weeks before ceasing and unable to recall dose.

October 2014

<u>buprenorphine/naloxone stabilisation</u>

Referred to DASSA by GP and Point of Engagement- an early intervention service for parents with substance use. ZT reported an increase in codeine use to 60 tablets (768mg codeine) after she ceased buprenorphine/naloxone in July 2014. She reported alcohol use of 100-150g daily. Inpatient stabilisation was advised due to risk of over sedation with alcohol use and risk of precipitated withdrawal. ZT refused inpatient admission. After negotiation outpatient stabilisation commenced with daily BAL of 0.00 prior to dosing and supervised daily dosing at DASSA clinic. ZT was informed of the risk of seizures, delirium tremens and death associated with abrupt cessation of alcohol. ZT stabilised on buprenorphine/naloxone with dose 32mg daily and was dispensed thiamine 100mg TDS daily.

She continued codeine but decreased to 30 to 60 tablets daily (384-768 mg), 3 to 4 days per week. Alcohol use decreased to 100 grams on 4 days per week.

February 2015

Pregnancy confirmed February 2015 and changed from buprenorphine/naloxone to buprenorphine.

ZT reported reduction of codeine and alcohol use 4 weeks before conception to 30 tablets ibuprofen-codeine (384 mg codeine) on 4 days per week and alcohol 80 grams daily 3 to 4 days per week.

March 2015

ZT had a complete miscarriage in March 2015 at 7weeks gestation. After the miscarriage ZT relapsed to increased use of 60 tablets ibuprofen-codeine (768g

codeine) on 2 occasions 1 week apart and alcohol increased to 200g daily. ZT was prescribed acamprosate with variable compliance.

ZT expressed her desire to conceive again and was advised to complete an inpatient withdrawal which she declined.

April 2015 to May 2015

Reported use of 30 tablets ibuprofen-codeine daily (384 mg codeine) and alcohol 100 grams daily.

June 2015

Reduced use of ibuprofen-codeine to 30 tablets daily on three days over the last 4 weeks. Reported alcohol use 100grams daily.

July 2015 to August 2015

Reduced use to 6 tablets ibuprofen-codeine daily (76.8mg codeine) and alcohol 40g on 3 days per week over the 4week period prior to confirmation of pregnancy in early August 2015.

ALCOHOL

ZT reported a 5 year history of alcohol dependence.

ZT reported alcohol use for most of her adult life in a binge pattern>60 grams per day up to three times per week and reported daily regular use for the last 5 years. She commenced regular alcohol use after she became dependent on codeine. She stated that codeine and alcohol use developed after she reduced her amphetamine

use. When she presented to DASSA in August 2014 she reported consumption of 1 to 1.5 litres wine daily (100-150grams alcohol).

There was an increase in her alcohol use in the month following her miscarriage in March 2015 triggered by emotional distress. ZT reduced alcohol use to 40 grams on 3 days per week during the 4week period before pregnancy was confirmed. This would have been during the time of conception.

The reported history of codeine and alcohol use fulfilled the criteria for substance dependence. ZT reported craving, compulsion, and use of both substances at different times to alleviate withdrawals that she identified as primarily codeine withdrawal. During admissions for inpatient withdrawal she had withdrawal symptoms from alcohol and codeine including rhinorrhoea, backache, diaphoresis, agitation, headache and diarrhoea. There was an increased tolerance to codeine and alcohol and ongoing use despite awareness of harms with use. There was a history of multiple attempts to decrease use over many years with therapeutic counselling and inpatient withdrawal episodes.

Two past DUI offences and associated MVA in 2005 and 2010.

AMPHETAMINE

ZT commenced use age 17 years with reported irregular use once to twice a fortnight. Her use increased from age 24 years when she lived with a dealer of amphetamines. She reported daily dependent intravenous use from 24-29 years but was unable to recall past quantities used. From 2010 at time codeine commenced she reported a decrease in use to 1 to 2 points intravenously once every 3 months.

Her last amphetamine use reported was in November 2014 one month after commencing buprenorphine/naloxone.

NICOTINE

ZT became nicotine dependent soon after she commenced tobacco smoking at age 15 years. She smoked 20-25 cigarettes daily. No periods of abstinence were reported. ZT reported a decrease from 25 to 15 cigarettes daily during pregnancy. She declined support and nicotine replacement therapy to further reduce nicotine use during pregnancy.

BENZODIAZEPINE USE

Nil

CANNABIS

Nil

PAST MEDICAL HISTORY

A past history of Domestic Violence.

No past history of loss of consciousness or seizures.

Nil known allergies.

June 2007

Attended hospital with closed head injury following physical assault- sustained # nasal bones and required plastic surgery.

October 2010

Motor vehicle Accident (DUI) sustained soft tissue injury to low back.

PAST OBSTETRIC HISTORY

G7P3

X2 Termination of pregnancy 1995 and 2005

November 2006	Complete miscarriage 7/40
November 2007	Normal vaginal delivery 38+6 Birth Weight(BW) 2870g
October 2013	Induction of labour 37+4/Intrauterine growth retardation(IUGR) BW 2310g and NAS
March 2015	Complete miscarriage 7/40
March 2016	Induction of labour 37weeks/IUGR BW 2485g

PAST PSYCHIATRIC HISTORY

Past diagnosis of Borderline Personality Disorder(BPD) in context of past childhood/adult trauma.

Age 15 years diagnosed with depression.

Age 21 years prescribed citalopram for 6 months.

Age 29 (2006) started deliberate self -harm(DSH) cutting after ceasing regular drug use. Attempted suicide by hanging while intoxicated with alcohol.

Age 33 (2010) Codeine abuse /dependence. DSH cutting wrists in front of parents when intoxicated with alcohol. Paracetamol over dose while intoxicated with alcohol

Anger issues prescribed duloxetine 100mg/d with reduction in irritability

Psychiatric assessment with diagnosis of Borderline Personality Disorder and referred for Dialectical Behavioural Therapy.

Reported never planned DSH or suicide, all impulsive acts at times of crisis while intoxicated with alcohol. DSH may have been used to alleviate intense emotional distress.

MEDICATION HISTORY

2009-2010 duloxetine 100mg /d

2010-2014 sertraline 200mg/d

2010-2015 quetiapine 400mg nocte

MEDICATIONS current

Thiamine 100mg TDS

Ceased quetiapine during second trimester of pregnancy.

PSYCHOSOCIAL HISTORY

Eldest of 3 children.

History of childhood emotional and physical abuse from parents.

Stated indifference towards mother but reported close to father.

1992-Age 15 years old parents separated, mother left the family home. She reported conflict with her stepmother

Completed Year 10 at high school and worked in retail.

1996-Age 19 sex work and 3 year DV relationship.

ZT left relationship after attempted strangulation.

1999-Age 22 Worked at fast food restaurant and lived with her mother.

2001-Age 24 used regular amphetamines IV. Her mother found a needle and she was asked to leave.

Worked as security guard from 25-28 years.

2005-Age 28 years MVA/DUI alcohol with loss drivers licence.

2006-Returned to sex work and met the father of her first child and became pregnant age 29/30 years. Victim of DV with fractured nose when 4 months pregnant.

Left relationship when daughter 6months old.

2010-At age 33 years, alleged sexual assault at party, DUI and MVA.

(commenced codeine subsequently)

2012-Age 35 years, new partner who was employed as car detailer.

Stated no DV.

2015-Age 38 years, stable accommodation caring for her 2 children age 7 and 19 months with partner who was father of second child born 2013 and father of case pregnancy.

FHX

Mother possible depression

PREGNANCY ASSESSMENT - August 2015

DASSA outpatient consultation

ZT reported planned decrease use of ibuprofen-codeine and alcohol use pre-conception with intention to cease use once pregnancy confirmed with goal to reduce risk of NAS.

LNMP 17/6/15- pregnancy confirmed approx. 5-6w gestation

MEDICATIONS

buprenorphine/naloxone 32 mg sublingual daily, thiamine 100mg TDS, quetiapine 300mg nocte, pregnancy multivitamin tablet one daily

SUBSTANCE USE

Alcohol 3 days per week during last 4 weeks-½ bottle wine on these days (30-40grams alcohol), last alcohol 40g 3 days ago.

Opioids-6 tablets ibuprofen-codeine(200mg-12.8mg) daily (77 mg codeine) used three days during last 4 weeks, last used 6 tablets 4 days previously.

Nicotine 20 cigarettes daily

Amphetamines reported last used end 2014.

PHYSICAL EXAMINATION

Weight 92kg, Height 166cm, BMI 33.4

No clinical evidence of intoxication or withdrawal from opioids or alcohol

BP 120/69, Hr 86

Pupils 2-3mm bilateral, no ophthalmoplegia

No pallor or jaundice

No diaphoresis or tremor

No track marks

No peripheral oedema

Normal gait, coordination intact

Abdominal, Cardiovascular and Respiratory exam unremarkable

Urine pregnancy test positive

BAC 0.00

MENTAL STATE EXAMINATION

Appearance – Female well groomed, looked stated age.

Behaviour- Appropriate and cooperative. Rapport easily established.

Cognition – Alert and oriented. Accurate recall of past events.

Mood- Normal range with mild anxiety.

Affect- Reactive and appropriate congruent with reported mood.

Thought process- Normal flow, no thought disorder.

Thought content-Some pre occupation with buprenorphine and risk of NAS.

Speech – Fluent, normal rate, volume and tone.

Insight- Appropriate, demonstrated by reported cessation of most substance use and prompt attendance after diagnosis for review.

Judgement- Not impaired. Demonstrated appropriate level of understanding of issues and acceptance of DASSA role regarding child protection.

Risk- Denied risk of self-harm or suicide. Denied risk of DV with partner.

PREGNANCY PROGRESS - August 2015 to confinement.

Buprenorphine/naloxone changed to buprenorphine at assessment in August 2015 when pregnancy confirmed.
Referred to DASSA antenatal drug and alcohol clinic at tertiary hospital and dating ultrasound arranged.

ZT remained focused on reducing her buprenorphine dose believing in an increased risk of NAS with buprenorphine use. She wanted to cease buprenorphine during pregnancy and maintain abstinence from codeine and alcohol thereby eliminating all risk of NAS.
Informed of the risks of relapse and increased risk of NAS, risk of precipitated withdrawal and resultant risk to the foetus.
Informed that there was no clear relationship between buprenorphine dose and risk of NAS.
She reported she had ceased all substance use except nicotine since pregnancy was confirmed.
Continued thiamine 100mg TDS PO for 2 months.

October 2015 – 14 weeks gestation
Negotiated slow reduction from second trimester with regular urine drug screens and evidence of abstinence from opiates/ other substances.

November 2015 – 18 weeks gestation

Buprenorphine reduced to 16mg daily and nicotine 20 cigarettes per day.

Continued buprenorphine reduction of 2 mg/week, monitored for withdrawal.

ZT reported mild withdrawal at 12 mg/day with rhinorrhoea and mild diarrhoea before dosing that ceased one hour after dosing.

ZT reported feeling mildly "high' 3-4 hours after dosing.

January 2016 – 25 weeks gestation

ZT requested split dosing. DASSA supported this request as stability demonstrated by:

>Regular attendance, no evidence of codeine used during pregnancy with x11 UDS buprenorphine only detected.

>Reported alcohol abstinence, BAC all negative and bloods supported this.

Authority from DDU provided (8mg mane supervised and 4mg nocte taken as unsupervised dose).

Reduced nicotine use to 15 cigarettes daily.

February 2016 – 33 weeks gestation

Decreased rate of buprenorphine reduction- 0.4mg increments.

Reduced from 12mg to 8mg in 5 weeks. Final total daily dose before delivery 6.4mg/day (4mg mane/ 2.4 mg nocte).

CONFINEMENT

Tertiary hospital

March 13th to 20th 2016

Admitted for induction of labour at 37 weeks gestation for growth retardation.

Spontaneous vaginal delivery live male 2485 grams, Apgar score 9 and 9.

Transferred to Neonatal Unit (NNU) for low birthweight and NAS observation.

ZT reviewed by DASSA CLS day 4 post -partum.

Increased buprenorphine to 8mg single dose daily.

No significant neonatal withdrawal observed.

Discharged home with infant day 6.

DASSA OPD

March 21st 2016 – 7 days post -partum

Reviewed at DASSA clinic by nurse and medical officer.

Reported full breast feeding, infant settled, gaining weight.

ZT requested increase buprenorphine to 10mg daily and transfer to buprenorphine/naloxone.

Assessed: tiredness within normal range for mother with newborn, mild mood lability.

Mid wife visits x2 over next 7 days.

March 28th 2016 - Review 2 weeks post-partum

Buprenorphine/naloxone increased to 12mg daily.

April 4th 2016 – 3 weeks post-partum

Buprenorphine/naloxone 24mg alternate daily

INVESTIGATIONS

1.PRIOR TO PREGNANCY

- UDS RESULTS

  25/6/15 and 2/7/15

  Opiates and buprenorphine detected

- BLOOD INVESTIGATIONS

  CBE and LFT/U&E June 2015, February 2015, March 2015 within normal limits

  BBV Screening December 2014

  Hepatitis A : total antibody not detected

  Hepatitis B : surface antigen not detected, surface antibody detected, core antibody not detected

  Hepatitis C: antibody not detected

  HIV EIA screen: non-reactive

2.ANTENATAL

- UDS RESULTS monthly UDS from August 2015 to March 2016

  All “buprenorphine detected only”

- September 2015 – 10 weeks gestation

  Antenatal Bloods: blood born virus screens negative.

  All other results normal.

- 21/1/16 Ultrasound

  Gestational age 28 weeks + 1 day

  “Normal morphology, normal growth parameters. S/D ratio 3.2 within normal limits.”

- 16/2/16 Ultrasound

  Gestational age 33 weeks +2 days

  Showed early indications of growth retardation (IUGR).

- 7/3/16 Ultrasound

  Gestational age 36 weeks

  Further signs of IUGR.

  SD ratio 3.8 above 95th percentile.

3.POST NATAL

- UDS 30/3/16 and 9/5/16

  “buprenorphine detected only”

- Placenta histology

  Macroscopic: Complete membranes, 3 vessels.

  Microscopic: Mild sub-chorionic and perivillous fibrin and features of chorangiosis present.

INTERPRETATION OF RESULTS

PRIOR TO PREGNANCY

UDS detected buprenorphine and opiates consistent with history of codeine use.

Mono acetyl morphine (a metabolite of heroin) was never detected

Blood investigations were within normal limits with no biochemical evidence of GI or renal complications associated with chronic NSAID use. There was no biochemical evidence of liver impairment associated with high alcohol intake. This may be due to a relatively short history of high level alcohol use.

BBV screening was negative and Hepatitis B s Ab consistent with past immunisation.

ANTENATAL

UDS results detected buprenorphine only, consistent with history.

Blood investigations remained within normal range.

BAL performed daily prior to dosing were negative.

Comparison of ultrasound scans from 16/2 to 7/3 /16 revealed growth retardation and an increased S/D ratio. Induction of labour was indicated at 37 weeks.

The S/D ratio is a measurement of resistance to blood flow in the umbilical artery.

The S/D ratio has been observed to increase when placental function is reduced and this is associated with IUGR. (1)

POSTNATAL

Placenta histology

Histology showed microscopic evidence of chorangiosis. Chorangiosis has been observed as a placental complication associated with maternal cigarette smoking and IUGR. (2)

Neonatal birth weight of 2485 grams was defined as low birth weight <2500 grams at delivery caused by IUGR.

DIAGNOSES (using ICD-10) and issues of concern

A 38year old woman with planned pregnancy prescribed buprenorphine/naloxone since 2014 for past opioid-codeine (ibuprofen/codeine OTC) dependence. There was a past history of polysubstance dependence and psychiatric co-morbidity.

Current

- OPIOID dependence-maintained on buprenorphine/naloxone then buprenorphine during pregnancy.

- ALCOHOL-dependence prior to pregnancy. Reported abstinence during pregnancy.
- NICOTINE dependence. This continued during pregnancy.
- Borderline Personality Disorder with features of anxiety and depressed mood.

Current pregnancy related risks and diagnoses

- G7P2
- Pregnancy planned with recent history of self-reported substance use during early weeks of gestation and potential risk to pregnancy, miscarriage, IUGR, NAS and FASD.
- Last pregnancy IUGR and NAS.
- Miscarriage 2015.

Past

- Past amphetamine dependence and abuse. Now in remission.
- Past self-harm and suicide attempt associated with high level emotional distress.

MANAGEMENT PLAN

ANTENATAL

This was a high risk pregnancy with history of maternal substance use maternal mental health problems and past pregnancy complications (IUGR and NAS).

Management included:

- Assisting client with maintaining abstinence from unsanctioned opioids, alcohol and amphetamine use and addressing nicotine dependence.
- Facilitating regular antenatal care.

This was achieved by a focus on engagement, provision of support and advocacy. A multi-disciplinary approach was used with DASSA liaison nurse as case worker co-ordinating comprehensive antenatal care at a tertiary hospital. There were regular reviews by DASSA nurse and doctor with monitoring of substance use and provision of relapse prevention therapy.

Mental health was monitored regularly by brief mental state examination and review of expectations and fears generally and specific to pregnancy.

Assessment of psychosocial stability and child safety was assessed at each review by monitoring of potential psychosocial stressors at home. This involved exploring issues regarding personal safety, relationship with partner, managing children and financial stability. There was regular assessment of risk of deliberate self -harm and suicidal ideation.

<u>POST PARTUM</u>

PSYCHOSOCIAL – Support provided by DASSA case-worker and linked with early intervention out -reach support service.

Continued monitoring of ZT and infant.

GENERAL HEALTH

Discussed contraception

Encouraged continued review with GP

INFANT

Encourage GP attendance for infant check and immunisations

Consider 6 month child development screen with paediatrician

DISCUSSION

This case raised a number of significant issues related to the pregnancy discussed, past pregnancy outcomes and the recent history of miscarriage.

The issues considered in this case discussion were those that were of primary concern to ZT.

1. BUPRENORPHINE USE IN CODEINE DEPENDENCE

ZT had a 5 year history of codeine dependence in the form of ibuprofen –codeine co formulation available OTC. There is risk of significant morbidity and mortality with long term ibuprofen-codeine use at supra therapeutic doses, primarily due to toxicity from high dose ibuprofen use. Complications include gastrointestinal disease with bleeding and anaemia, and renal complications resulting in renal failure and severe hypokalaemia. There was no evidence of these side effects in ZT but she developed codeine dependence and this is a recognised complication of long term ibuprofen-codeine use. (3,4)

The risk of developing codeine dependence may be associated with variability in metabolism of codeine to morphine. This conversion of codeine to morphine involves the process of O-demethylation by the liver enzyme cytochrome CYPp450 2D6. There is wide genetic variation in the expression of the CYPp450 2D6 gene with 74 alleles reported. (5) These alleles convey a wide variation of enzyme activity from no activity to ultrarapid metabolism. (6) Population studies of the European Caucasian population show variability in metabolism with up to 7-10 % poor metabolisers and 5% ultrarapid metabolisers. It has been proposed that the fast

metaboliser group are at greater risk of developing dependence because they have increased conversion of codeine to morphine with increased opioid effects. (3) ZT had an additional increased risk of sedation and respiratory depression due to her alcohol dependence.

The OTC co formulation of ibuprofen-codeine is currently PBS listed as schedule 3. (7) The ease of availability of this medication may increase the potential for abuse and dependence in vulnerable populations. It also results in difficulties in monitoring use on an individual and population level in comparison to prescribed morphine formulations where PBS scripts for an individual can be tracked. ZT reported that she spent considerable time travelling to different pharmacies to purchase the medication to avoid arousing suspicion of her dependence. The TGA has recognised these risks and responded by “up- scheduling” schedule 2 and 3 codeine formulations to schedule 4 from February 2018. (7)

Although methadone has been available for opioid pharmacotherapy since 1969 there is substantial evidence that buprenorphine/naloxone is effective and comparable to methadone. (8,9) Codeine is a relatively weak opioid and buprenorphine/naloxone was chosen because of its partial agonist effects at the mu opioid receptor in comparison to methadone which has complete agonist effects. Buprenorphine/naloxone maintenance has been used as first line treatment for codeine dependence. (4)

Buprenorphine/naloxone was chosen in preference to methadone because of its partial opioid agonist effect at the mu opioid receptor resulting in maximal opioid effects that reach a ceiling effect at higher doses. This provides a potentially wider margin of safety against increased sedation and respiratory depression compared to methadone a full mu agonist. (10,11) Buprenorphine/naloxone was considered the safer maintenance therapy compared to methadone for ZT who had additional risks of sedation and respiratory depression from alcohol dependence. Alcohol use was monitored by daily BAC prior to dosing and periodic biochemical testing to compare gamma-glutamyl transferase(GGT) and transaminases and these remained within normal range. Use of random BAC may have provided a more representative picture of current alcohol use but due to ZT being reliant upon public transport and caring for 2 young children this was not practical. The utilisation of other markers of chronic alcohol use including measurement of urine ethyl glucuronide (ETG) and serum carbohydrate deficient transferrin (CDT) are not routinely used in our community based treatment setting. In this case CDT measurement may have been of limited value as it can be affected by hormone levels in women and may be elevated during pregnancy. (12)

2. BUPRENORPHINE USE IN PREGNANCY

ZT was initially focused on decreasing and ceasing opioid maintenance due to her concerns of Neonatal Abstinence Syndrome(NAS). ZT agreed to defer reduction of her buprenorphine dose until after the first trimester and to provide negative UDS results confirming no lapse to codeine use. This negotiation was necessary to maintain her engagement with the service and remain in treatment. Withdrawal

from opioids is not recommended during pregnancy. Dose reductions where they do occur, need to be carefully managed to avoid opioid withdrawal. The risk of buprenorphine reduction during the first trimester included relapse to opioid use and miscarriage. Opioid withdrawal during the third trimester is associated with fetal distress and death. (8)

There is a lack of evidence regarding the safety of buprenorphine/naloxone use during pregnancy with limited human studies. One retrospective small study examining the use of buprenorphine/naloxone during pregnancy found no significant adverse maternal or neonatal outcomes. (13) The recommendation is that pregnant women prescribed buprenorphine/naloxone should be transferred to the buprenorphine mono formulation due to the potential of naloxone precipitating opioid withdrawal in the fetus. (8,9,14)
The safety of buprenorphine in pregnancy has been demonstrated in multiple studies but there is limited data available regarding the pharmacokinetics of buprenorphine during pregnancy.(14,15,16)

The major focus for ZT was reducing risk of NAS. NAS is a group of withdrawal symptoms that occur in the neonate following chronic exposure in utero to a number of substances including opioids, ethanol, amphetamines and nicotine. The clinical features of NAS are associated with signs of increased irritability of the central nervous system and gastrointestinal systems, respiratory distress and vague autonomic symptoms including nasal stuffiness, yawning, skin mottling and fever.

The modified Finnegan's Scale is a validated scoring system to assess NAS in infants exposed to opioids delivered at term or near term. (9,17)
Methadone and buprenorphine have similar efficacy and similar rates of NAS with occurrence in approximately half of cases. Buprenorphine is associated with less severe NAS and shorter length of stay in hospital compared to methadone. No harmful effects in utero have been found with use of buprenorphine. (15)

ZT remained focused on reducing her buprenorphine dose believing that it would reduce the risk of NAS. There appears to be no relationship between buprenorphine dose and NAS severity. (16,18) The factors affecting variability in the incidence and severity of NAS have not been clearly identified. Risk factors thought to affect clinical presentation and severity of NAS include a history of polysubstance exposure and neonatal genetic variation of the minor alleles in the mu opioid receptor and catechol-O-methyltransferase genes. (19)

During the second trimester of her pregnancy ZT had reduced her dose from 32mg daily to 12mg daily. At 12mg daily that ZT reported mild withdrawal symptoms that settled 1 hour after dosing. This effect was probably due to the reduced terminal half-life of buprenorphine seen with doses of less than 16 mg daily and the reduced duration of action as buprenorphine levels decrease to cause some withdrawal symptoms. At very low doses terminal half-life may range from 8 to 12 hours compared to 24 to 72 hours observed for doses above 16 mg daily. (10,11) ZT reported feeling mildly "high" 3 to 4 hours post dose when peak dose effect would be expected to occur. One possible explanation was that buprenorphine levels may

fall sufficiently at trough, resulting in a relative decrease in tolerance with increased opioid effects experienced when dosed.

There is limited information regarding the pharmacokinetics of buprenorphine during pregnancy. It has been suggested that the dose may need to be increased during pregnancy, (16) with one series reviewing 45 patients reporting an increase in dose required during the mid-trimester. (20) Smaller sized studies have demonstrated a significant change in buprenorphine pharmacokinetics during pregnancy, (21) and changes in metabolism shown by decreased drug concentration associated with increased activity of glucuronidation enzyme activity. (22)

After approval was given by the Drugs of Dependence Unit (DDU) for split dosing ZT reported no further “withdrawal” symptoms and no “high” post dose. She continued to reduce by 0.4mg and her dose prior to delivery was 6.4mg daily in a split dose of 4mg mane and 2.4mg nocte.

3. BUPRENORHINE AND BREASTFEEDING

Breast feeding has been shown to promote mother and infant attachment and provide health benefits to mother and infant. Experimental evidence suggests that breast feeding may protect against depression in the mother during the postpartum period. The hormones oxytocin and prolactin are thought to be associated with anxiolytic and antidepressant effects by reducing the cortisol response to stress. (23) Oxytocin may be an important factor in bonding between mother and infant. The maternal release of oxytocin centrally is stimulated by multiple sensory modalities;

tactile including nipple stimulation by feeding, visual, auditory and olfactory. (24) It has been shown that NAS severity is reduced by skin to skin contact, rooming in and breast feeding, and that those infants with low scores can be managed by these techniques alone. (25) With a past history of borderline personality disorder ZT was at risk of postpartum depression or post-partum mood disorder. ZT was motivated to breast feed and this may reduce her risk of her developing a postpartum mood disorder.

Buprenorphine has poor oral bioavailability resulting from extensive first pass metabolism. The small amounts of buprenorphine and its metabolite nor-buprenorphine that may be excreted in breast milk and ingested by the neonate are expected to have minimal effect. This is supported by studies showing that NAS is not prevented when infants are exposed to buprenorphine from mothers during breast feeding and breast fed infants exposed to buprenorphine do not develop symptoms of NAS when feeding is ceased. Although the levels of buprenorphine in the neonate are very low it may be that this in addition to other properties in breast milk has an effect on the maternal infant bond that may decrease the severity of NAS. (25,26) It is interesting that buprenorphine is not recommended in breastfeeding by the manufacturer though it is recommended and continued in clinical practice. (8)

There is no evidence regarding the safety of naloxone when taken in the buprenorphine/naloxone combination during breast feeding. Limited pharmacokinetic studies have found no significant amounts of naloxone absorbed sublingually because of the low bio-availability of naloxone via this route. (27) The

National Guidelines for Medication assisted Treatment for Opioid Dependence advise that during breast feeding the absorption of naloxone would be at such low levels that the effects on the neonate would be insignificant. (8)

The Drugs of Dependence Unit (DDU)is the South Australian regulatory body that administers parts of the controlled Substances Act. There is no specific policy by the DDU regarding authority for buprenorphine mono during breast feeding. The DDU reported no neonatal safety concerns regarding the use of buprenorphine/naloxone during breast feeding, consistent with clinical practice guidelines. (8)

Following delivery ZT requested transfer to daily dose buprenorphine followed by transfer to the buprenorphine/naloxone formulation one week later. Her dose increased to 12mg daily and she changed to 24mg alternate daily dosing one month after delivery.

4. CHILD PROTECTION

For the duration of pregnancy ZT engaged well with DASSA services and was adherent with opioid pharmacotherapy. Her goal was to reduce and cease her unsanctioned opioid and alcohol use and she achieved this. When attending appointments her children presented well and interactions were appropriate. Her partner shared child caring after hours and there was no reported or suspected domestic violence. There were no child protection concerns for the duration of pregnancy but ongoing monitoring continued due to the significant risk of relapse post-partum.

CONCLUSION

In this case ZT had a history of polysubstance use and achieved abstinence from alcohol and codeine use during pregnancy. She was not able to achieve abstinence from nicotine use with behavioural therapy and was not interested in using low dose intermittent NRT during pregnancy. (9) This case demonstrated pregnancy as a time when there can be motivation for significant change to substance use. In studies of pregnant women who used illicit substances before pregnancy higher rates of abstinence from illicit substances and alcohol and lower rates of abstinence from nicotine have been observed. (28)

In this case ZT was motivated to reduce the risk of NAS with her focus to cease opioids and alcohol. She may have perceived nicotine as less harmful. The outcome for ZT was favourable with no significant NAS experienced by her newborn though there was evidence of IUGR and low birth weight associated with continued nicotine use. (9)

ZT is at high risk of relapse post -partum due to her history of polysubstance dependence, (28) and psychosocial stressors that have been a trigger for relapse to use in the past.

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The Royal Australasian College of Physicians

Adult Medicine Division

Australasian Chapter of Addiction Medicine Training Program

Marking Sheet for Case Histories

Date [redacted]

Name of trainee: [redacted]

Title of case history: Case Involving Opioid Substitution during Pregnancy

The Case History should be approached as though it were being presented to a consultant at a ward round. That is, all relevant information should be included along with any relevant negatives. The trainee should have thought through the diagnoses and be able to discuss them and propose investigation and management relevant to Addiction Medicine.

The Case History must receive a *Satisfactory* result against the majority of marking criterion in order for the Case History to receive an overall result of *Satisfactory*.

Type of Case History

1. Is the category of Case History specified: **Yes** ☑ **No** ☐

If so, please tick the relevant category below:

- ☑ Consultation liaison case for general hospital setting
- ☐ Case report of treatment of an adolescent
- ☐ Case involving psychiatric morbidity
- ☐ Case involving medical comorbidity
- ☐ Case involving significant social issues such as criminality, forensic issues, child protection, issues relating to CALD populations and third party compensation
- ☐ Case involving continuing direct patient care over at least 3 months

2. Is the reason why Addiction Medicine was contacted specified? **Yes** ☑ **No** ☐

Comments: No comment to make here

History	Satisfactory	Unsatisfactory
The trainee details the symptoms of the patient	☑	☐
The trainee details the drug use history	☑	☐
The trainee details the treatment history	☑	☐
The trainee has detailed a general medical history	☑	☐
The trainee has described a psychiatric history	☑	☐
The trainee has included a psychosocial history	☑	☐

Examination	Satisfactory	Unsatisfactory
The trainee describes findings from the physical examination	☑	☐
The trainee describes findings from the mental state examination	☑	☐

Investigations	Satisfactory	Unsatisfactory
The trainee has described and appropriately interpreted investigations conducted	☑	☐

Discussions	Satisfactory	Unsatisfactory
The trainee has put together an appropriate formulation, including diagnosis of the patient	☑	☐
The trainee has described the short-term management of the patient	☑	☐
The trainee has discussed the long term management of the patient	☑	☐
The trainee has discussed with reference to appropriate literature	☑	☐

Style and Lucidity The structure, quality and style of writing are expected to be of a standard suitable for submission to a peer reviewed journal or research ethics committee	YES	NO
The case history has been written in third person.	☑	☐
The case history has been clearly presented	☑	☐
The case history is within the specified word limit of 5000 words.	☑	☐

word count not provided therefore cannot confirm if within 5000 word limit

Overall assessment	Satisfactory	Unsatisfactory
	☑	☐

General Comments:

- Excellent presentation of case study. Clinical case relevant and a good choice for this assignment.
- Thorough pertinent discussion and well referenced
- Presentation of investigations and findings on examination – being predominantly point form – appropriate for presentation at a clinical meeting but would need to be in a more narrative form for submission for publicatio

[redacted]

Please email form to: AddictionMedTraining@racp.edu.au

Or post to:

Education Officer for Addiction Medicine
Royal Australasian College of Physicians
145 Macquarie Street
Sydney NSW 2000