Joint BAP NAPICU Evidence Based Guidelines for
The Clinical Management of Acute Disturbance
(De-escalation and RT)

Hot Topics: Rapid Tranquillisation in Other Clinical Scenarios

Pregnancy & RT

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Declaration of interests

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napicu
national association of psychiatric intensive care & low secure units

NHS
Central and North West London
NHS Foundation Trust

Prescribing RT in Pregnancy

- Prescribing for women
  - Prescribing for pregnant women
    - Prescribing for acute mental illness in pregnant women
      - **Prescribing RT for pregnant women**

Prescribing for Women

Pharmacodynamics & Pharmacokinetics

Physiological differences between men and women

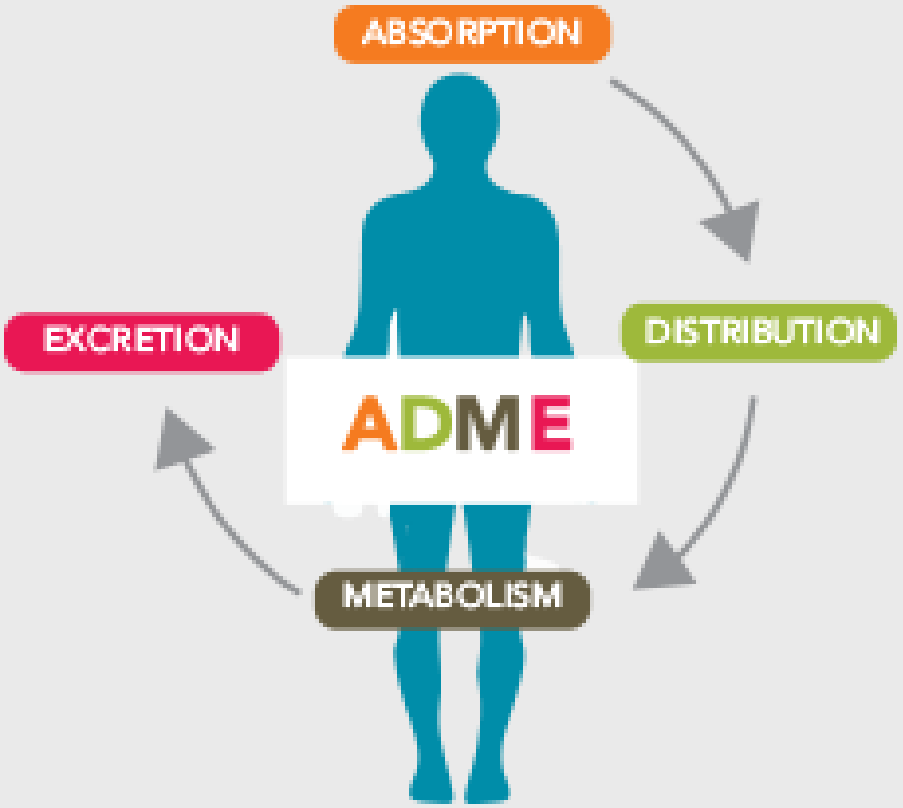
Parameter	Relative difference in women
QTc prolongation	Longer QTc: (by 2-6%) ↑ risk of Torsade de Pointes
% body fat	Higher: Women tend to have a greater percentage body fat which increases the volume of **distribution** of lipophilic drugs, allowing accumulation in adipose tissue over time
% body water	Lower: affects drugs that distribute in water e.g. Lithium
Gut motility	Slower: reduced gastric acid secretion and a delay in the **absorption** of drugs from GIT can reduce bioavailability and delay achieving therapeutic drug plasma levels
Metabolism	Reduced hepatic enzyme activity delays drug **metabolism**
Renal blood flow and GFR	Lower: reduced GFR

[i] Schwartz JB. The influence of sex on pharmacokinetics. *Clin. Pharmacokinet* 2003; **42**(2): 107–121.

Prescribing for Women

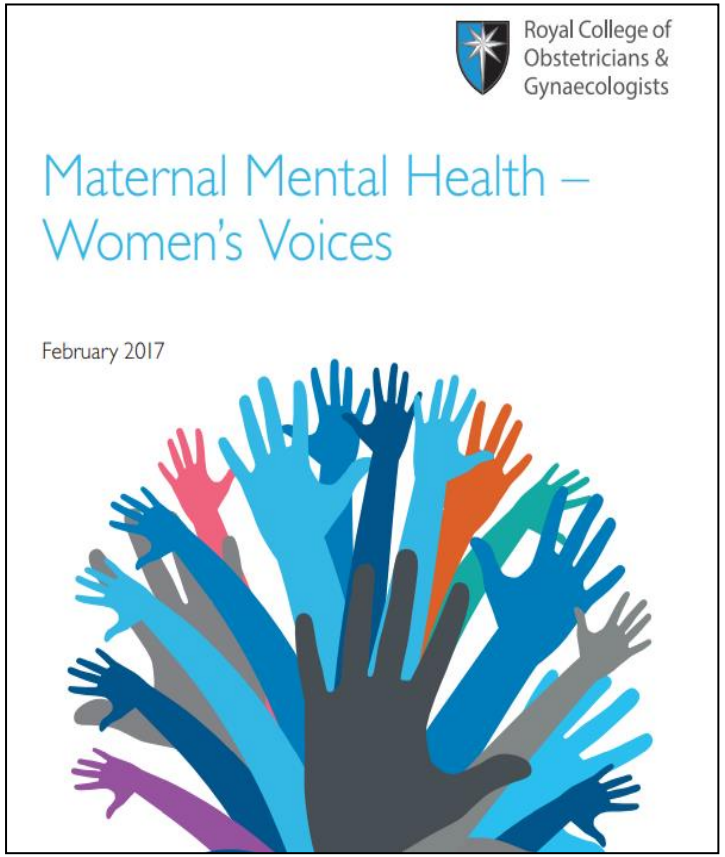
Pharmacodynamics & Pharmacokinetics

Physiological differences between men and women



- **All stages** of pharmacokinetics can **differ** between men and women
- Differences in **METABOLISM** have the most impact on prescribing
- ADME will effect **therapeutic response** and **adverse effects** experienced

Prescribing in Pregnancy - women's views



Those who were previously on medication for their mental health received inconsistent and conflicting advice from healthcare professionals about whether to continue or stop.

A number of women reported being given unhelpful advice or no advice at all about their medication.

One respondent reported that her perinatal psychologist considered that the benefits of her medication outweighed the risks to the baby, while a crisis team psychiatrist told her that her medication was hurting her baby. She also faced difficulties when trying to obtain her medication, with her GP reluctant to prescribe her medication and one pharmacist refusing to fill the prescription.

Prescribing in Pregnancy - women's views

Professionals are still giving unclear and inadequate advice about the risks of medicines to women who are or may become pregnant.

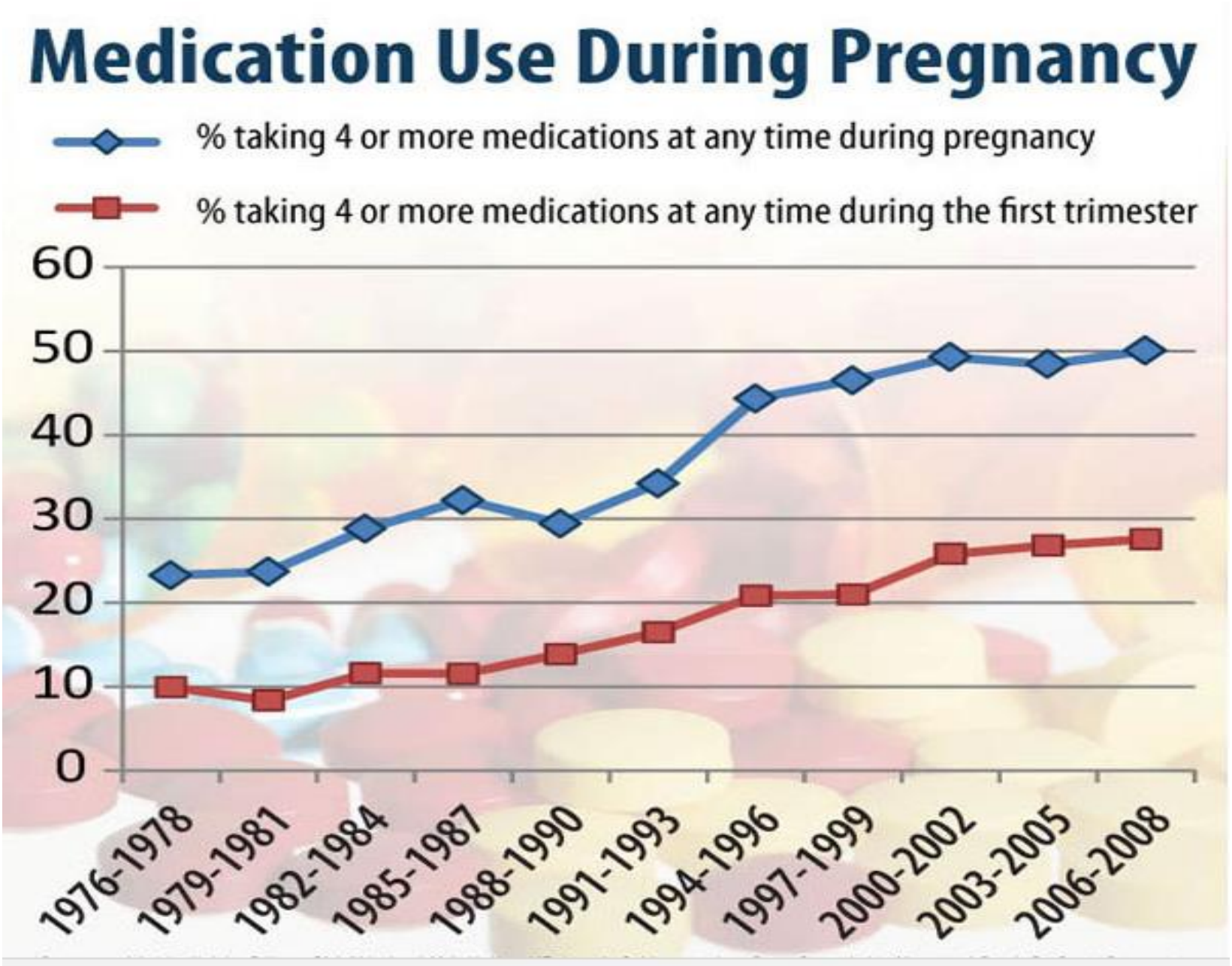
Prescribing for women –
Lack of data: Women in clinical trials

- Most medicines are generally tested in men
- Analysis of 150 depression trials from 2007[1]: 15% didn't report gender breakdown of participants, 50% didn't analyse by gender
- In a study of 768 trials[1], 89% reported recruitment of both men and women, but <1% analysed results by gender
- JAMA & BJPsych 2012-2015 728 paper, 16% stratified by gender, only 4% did an interaction test for gender[2]
- Women are often excluded from trials indirectly
  - due to menstrual cycle changes, use of hormonal treatments
  - **pregnancy** and lactation

1. Weinberger AH, Mackee SA, Mazure CM. Inclusion of women and gender-specific analysis in randomised clinical trials of treatments for depression. J Womens' Health 2010; 19: 1727-1732.
2. Howard LM, Ehrlich AM., Gamlen F, Oram S. Gender-neutral mental health research is sex and gender biased. Lancet 2017; 4: 9-11.

Prescribing in Pregnancy - General recommendations

- Women with pre-existing mental health conditions are at risk of relapse during pregnancy (NICE 2014c)
- Ideally avoid medicines in pregnancy
  - When not possible many guidelines recommend treating the mother as per usual clinical algorithms (NICE 2015b; NICE 2014c)



Taken from https://www.cdc.gov/pregnancy/meds/treatingfortwo/data.html

Prescribing in Pregnancy – Principles to consider

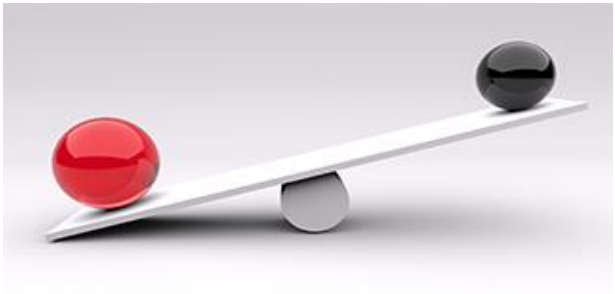
- **Pharmacological and pharmacokinetic changes**
  - variations in clearance between trimesters;
  - increased glomerular filtration rate;
  - expansion of plasma volume
    - which subsequently returns to pre-pregnancy states soon after delivery
  - Avoiding drugs that may accumulate in both maternal and foetal tissues is an advisable precautionary measure; for example by not prescribing oral diazepam and selecting medication with a short half-life (McAllister-Williams et al., 2017).

Prescribing in Pregnancy –
Principles to consider
Risk vs Benefit

→ Minimal evidence in pregnant population
- NO treatment isn't better = untreated illness
- extrapolate in absence of data

– Direct risks
- Growing evidence to show that untreated mental illness can lead to adverse effects in the unborn child

– Indirect risks
- Risk taking behaviour
- Poor bonding
- Poor self care



Prescribing in Pregnancy – Principles to consider

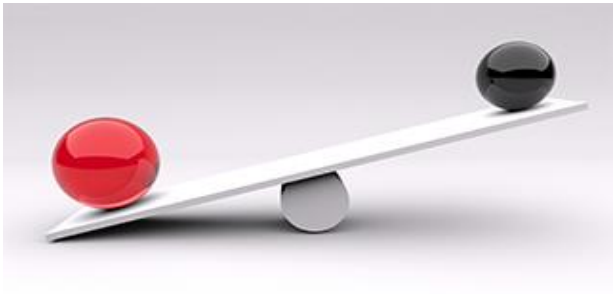
Treating

- Medication risks to the foetus
- May ↑ baseline risk of structural malformations (1st trimester)
- May affect foetal development, growth defects
- May lead to complications at birth (3rd trimester).
  - includes floppy baby syndrome with benzodiazepines
  - Includes EPS with antipsychotics
- ↑ risk of teratogenicity if multiple medicines
- In 2nd & 3rd trimesters organs such as the cerebral cortex and renal glomeruli continue to develop and remain particularly susceptible to damage
- Teratogenic effects are usually dose-dependent, the dose response curve is steep

Weighing up

Not treating

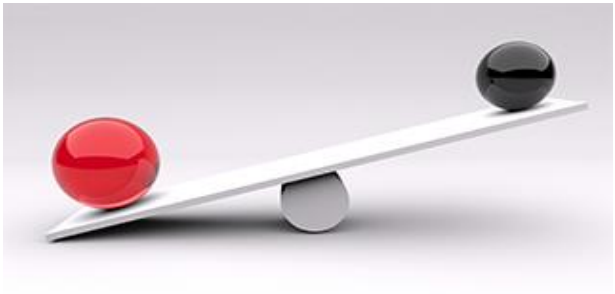
- Risks to the foetus/ neonate if the mother's mental illness relapses due to no treatment



Prescribing in Pregnancy –
Principles to consider
How do you decide on the risk?

Individual

- What happens when she becomes unwell?
- How serious is her illness?
- What has been tried in the past?
  - Medications & non-drug options
- What is her current treatment?
- What are the treatment options?



Prescribing in Pregnancy – Principles to consider

- If you are not sure of the evidence
  - Ask for advice
- Give the information in the best available format to help the woman make decisions
- Where to go for information?

Psychopharm

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SAGE

British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017

R Hamish McAllister-Williams[1,2], David S Baldwin[3,4], Roch Cantwell[5], Abby Easter[6], Eilish Gilvarry[2,7], Vivette Glover[8], Lucian Green[9], Alain Gregoire[3,10], Louise M Howard[11,12], Ian Jones[13], Hind Khalifeh[11,12], Anne Lingford-Hughes[14], Elizabeth McDonald[15,16,17], Nadia Micali[18], Carmine M Pariante[12,19], Lesley Peters[20], Ann Roberts[20,21,22], Natalie C Smith[23], David Taylor[12,24], Angelika Wieck[25,26], Laura M Yates[27,28] and Allan H Young[12,19]; endorsed by the British Association for Psychopharmacology

Abstract

Decisions about the use of psychotropic medication in pregnancy are an ongoing challenge for clinicians and women with mental health problems, owing to the uncertainties around risks of the illness itself to mother and fetus/infant, effectiveness of medications in pregnancy and risks to the fetus/infant from in utero exposure or via breast milk. These consensus guidelines aim to provide pragmatic advice regarding these issues. They are divided into sections on risks of untreated illness in pregnancy; general principles of using drugs in the perinatal period; benefits and harms associated with individual drugs; and recommendations for the management of specific disorders.

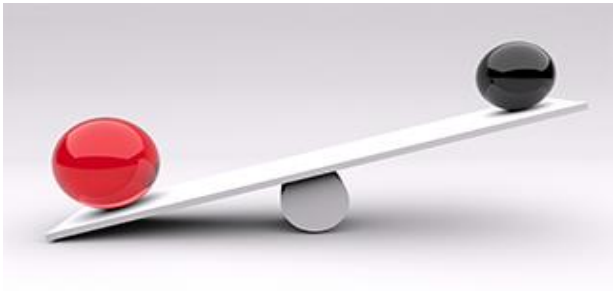
Prescribing RT in Pregnancy – The evidence

- A retrospective case series (n=80), 39% of pregnant women received oral (pre-RT) or IM (RT) medication for agitation in the USA emergency department; the authors did not make any active recommendations as to what to use (Ladavac et al., 2007).

Prescribing RT in Pregnancy – Principles to consider

Weighing up

- Relative risks of medicine A vs medicine B vs untreated
  - paucity of data
  - confounders such as concurrent medication, lifestyle & the illness
- All medicine concerns relate to *ongoing use*, not single doses
- Direct effects of RT on the neonate are likely to be minimal
- The risks associated with use of restraint and any ongoing regular medicines are likely to be more significant
- Lots of other considerations such as restraint positions (not prone or supine but semi-seated), techniques and equipment (e.g. use of beanbags) and suitable injection sites (gluteal or lateral thigh)



(NICE, 2015b; McAllister et al., 2017)

Prescribing RT in Pregnancy – Recommended medicines

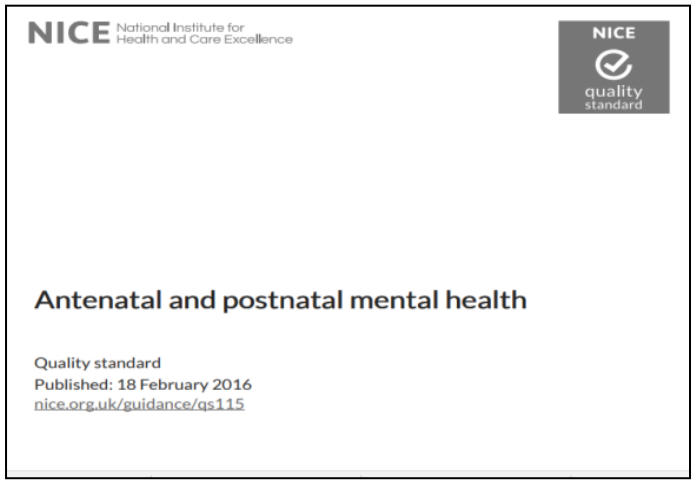
- IM **lorazepam**, **haloperidol** & **promethazine**
- No evidence to suggest these should not be used in a pregnant woman
- Absence of specific efficacy data in this population, so it is recommended that these agents are used
  - as per recommendations for non-pregnant women
- No license contraindication

Prescribing in Pregnancy – Benzodiazepines

- **Teratogenicity** - studies are conflicting about a possible association with increased risk of congenital malformation, specifically of orofacial clefts
  - Older studies suggest possible increased risks of congenital malformation, including orofacial clefts and cardiac malformations.
  - More recent, better designed studies, have failed to identify such associations.
- Oral lorazepam is specifically contraindicated in pregnancy https://www.medicines.org.uk/emc/product/6137

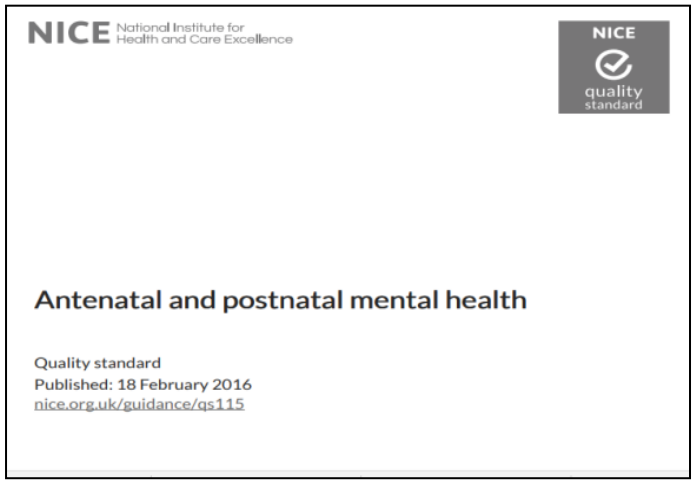
Prescribing in Pregnancy – Benzodiazepine withdrawal

- Risks of taking long term benzodiazepines when pregnant include withdrawal in the infant and floppy baby syndrome if they are used to term
- Stop gradually to reduce the risk of serious discontinuation symptoms



Prescribing in Pregnancy – Antipsychotics

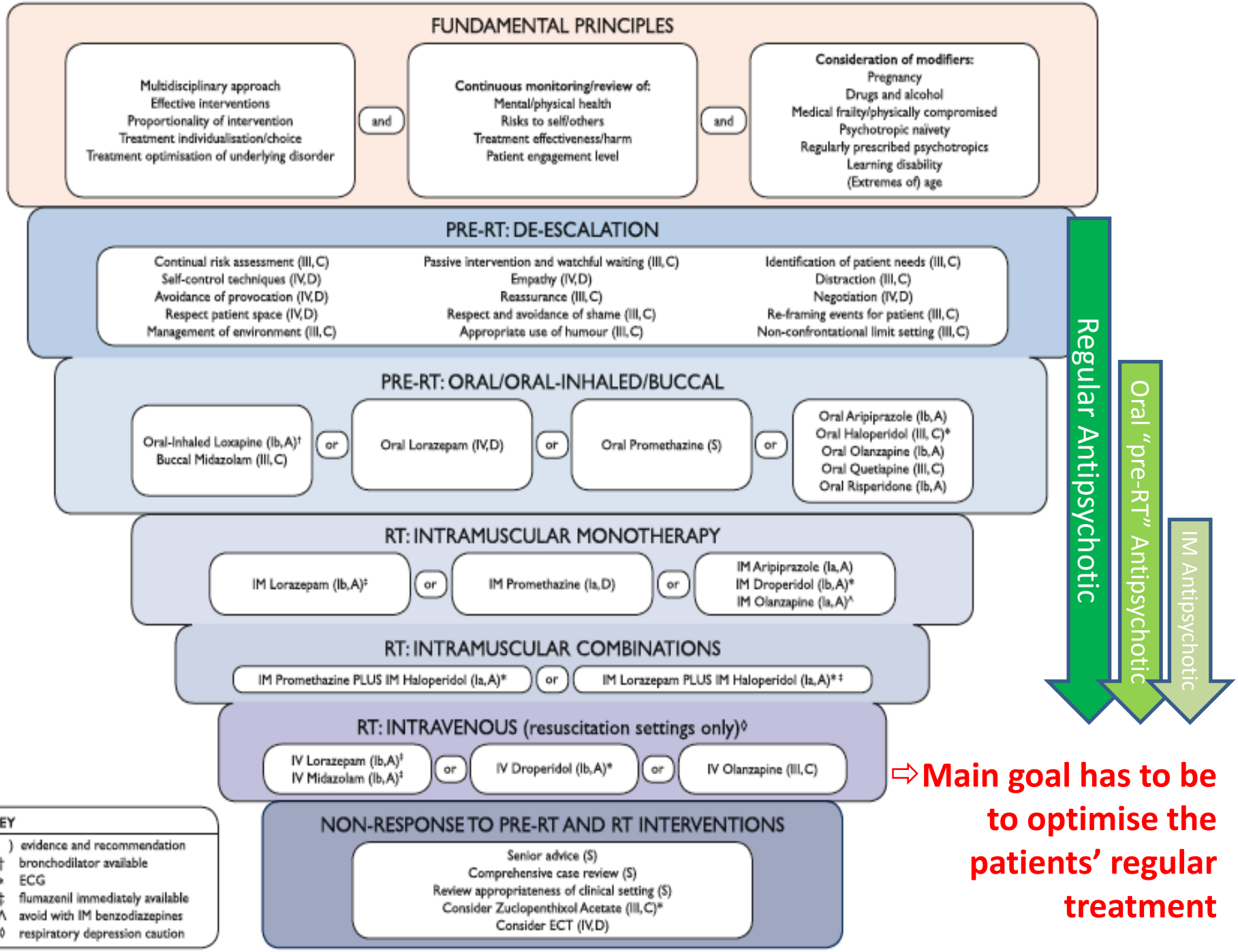
- Overall the data for the majority of antipsychotics do not suggest increased risk of major malformations or adverse foetal outcomes
- Consider side effects, particularly metabolic



Prescribing in Pregnancy – Promethazine

- Several recent meta-analyses and guidelines have concluded that promethazine is safe to use pregnancy in the ongoing management of nausea and hyperemesis gravidarum and recommend it.
- *"A number of dopamine antagonists may be used to treat NVP: phenothiazines (eg, chlorpromazine, perphenazine, prochlorperazine, promethazine, and trifluoperazine), domperidone, droperidol, metoclopramide, and trimethobenzamide. Anecdotal case reports have associated first trimester phenothiazine use with major malformations. However,* ***the bulk of evidence suggests that phenothiazines show no evidence of teratogenicity…..****"*

Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol 2002;186 Suppl 2:S256–61.
http://download.xuebalib.com/xuebalib.com.24865.pdf
The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum"
2016. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf
Full NICE guideline CG62 "Antenatal care routine care for the healthy pregnant woman"


FUNDAMENTAL PRINCIPLES
Multidisciplinary approach
Effective interventions
Proportionality of intervention
Treatment individualisation/choice
Treatment optimisation of underlying disorder
and
Continuous monitoring/review of:
Mental/physical health
Risks to self/others
Treatment effectiveness/harm
Patient engagement level
and
Consideration of modifiers:
Pregnancy
Drugs and alcohol
Medical frailty/physically compromised
Psychotropic naïvety
Regularly prescribed psychotropics
Learning disability
(Extremes of) age
PRE-RT: DE-ESCALATION
Continual risk assessment (III, C)
Self-control techniques (IV, D)
Avoidance of provocation (IV, D)
Respect patient space (IV, D)
Management of environment (III, C)
Passive intervention and watchful waiting (III, C)
Empathy (IV, D)
Reassurance (III, C)
Respect and avoidance of shame (III, C)
Appropriate use of humour (III, C)
Identification of patient needs (III, C)
Distraction (III, C)
Negotiation (IV, D)
Re-framing events for patient (III, C)
Non-confrontational limit setting (III, C)
PRE-RT: ORAL/ORAL-INHALED/BUCCAL
Oral-Inhaled Loxapine (Ib, A)†
Buccal Midazolam (III, C)
or
Oral Lorazepam (IV, D)
or
Oral Promethazine (5)
or
Oral Aripiprazole (Ib, A)
Oral Haloperidol (III, C)*
Oral Olanzapine (Ib, A)
Oral Quetiapine (III, C)
Oral Risperidone (Ib, A)
RT: INTRAMUSCULAR MONOTHERAPY
IM Lorazepam (Ib, A)‡
or
IM Promethazine (Ia, D)
or
IM Aripiprazole (Ia, A)
IM Droperidol (Ib, A)*
IM Olanzapine (Ia, A)^
RT: INTRAMUSCULAR COMBINATIONS
IM Promethazine PLUS IM Haloperidol (Ia, A)*
or
IM Lorazepam PLUS IM Haloperidol (Ia, A)*‡
RT: INTRAVENOUS (resuscitation settings only)◊
IV Lorazepam (Ib, A)†
IV Midazolam (Ib, A)‡
or
IV Droperidol (Ib, A)*
or
IV Olanzapine (III, C)
NON-RESPONSE TO PRE-RT AND RT INTERVENTIONS
Senior advice (5)
Comprehensive case review (5)
Review appropriateness of clinical setting (5)
Consider Zuclopenthixol Acetate (III, C)*
Consider ECT (IV, D)
KEY
( ) evidence and recommendation
† bronchodilator available
* ECG
‡ flumazenil immediately available
^ avoid with IM benzodiazepines
◊ respiratory depression caution
Regular Antipsychotic
Oral "pre-RT" Antipsychotic
IM Antipsychotic
⇨Main goal has to be to optimise the patients' regular treatment