Beattie Smith Lecture
May 2019

Women's Mental Health is not a National Priority

NOT GOOD ENOUGH!

Professor J.KULKARNI
Monash Alfred Psychiatry
Research centre
www.maprc.org.au

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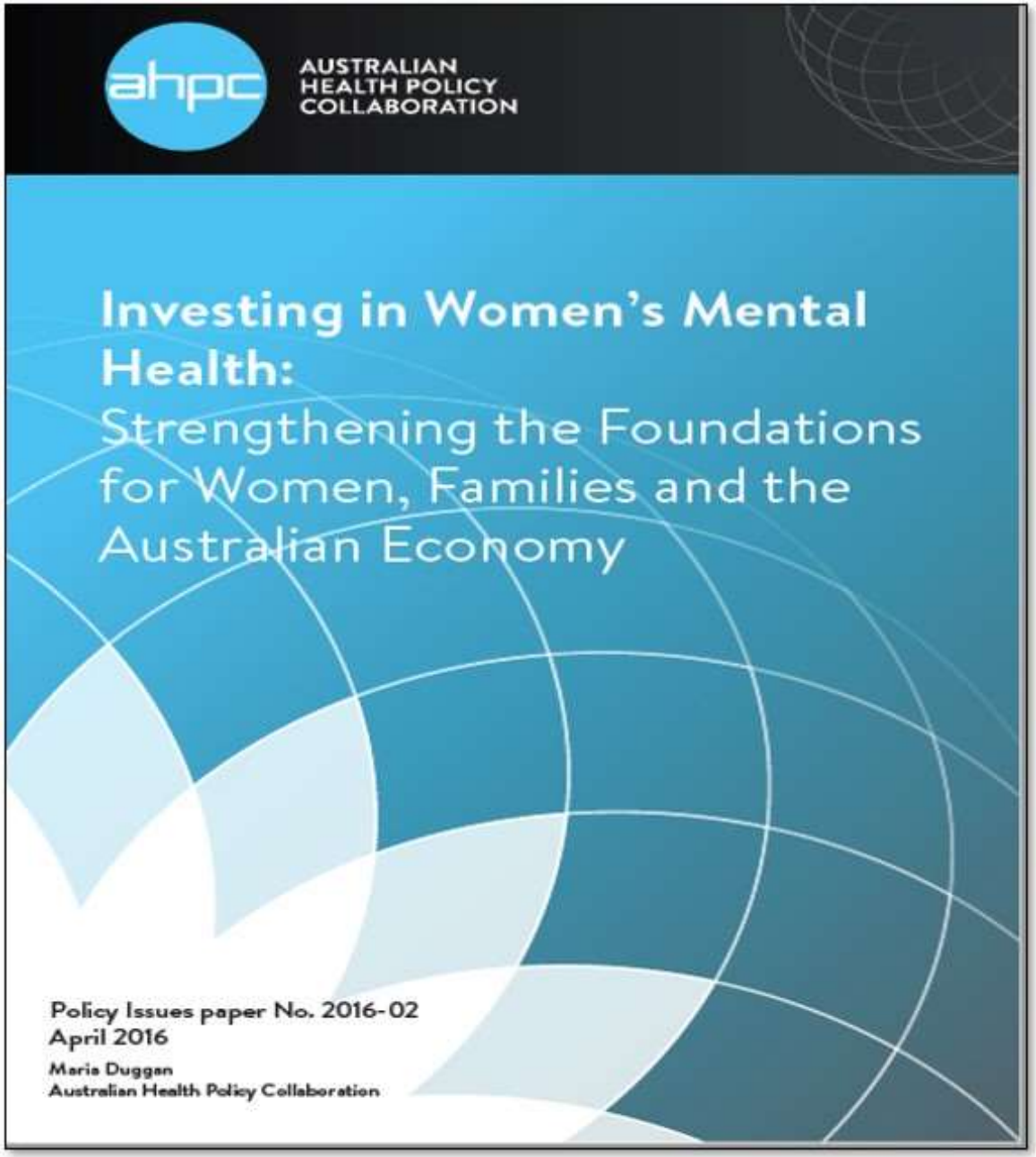
"Mental health policy in Australia is gender-blind and does not consider women's mental health across the life course".

Duggan, M. (2016) Investing in Women's Mental Health. Strengthening the foundations for women, families and the Australian economy. Australian Health Policy Collaboration Issues paper No. 2016-02. Australian Health Policy Collaboration, Melbourne



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Mental Illness in Australian Women

- Mental disorders represent the leading cause of disability and the highest burden of non-fatal illnesses for women in Australia
- 43% of women (3.5 million) have experienced mental illness at some time.

AIHW 2014

Mental Illness in Australian Women

- Australian women are more likely than men to have experienced symptoms of a mental disorder during the previous 12 months (22% of women compared to 18% of men)
- Young women report the highest rates of mental disorder of any population group (30% for women aged16 to 24)

AIHW 2014

Mental Illness in Australian Women

Women are more likely than men to have (or report symptoms of) the following conditions:

- Anxiety disorders – 18% (11% of men)
- Affective disorder such as depression - 7% (5% of men
- Eating disorders – 15% of young women have had an eating disorder at some point in their lives, and the third most common chronic illness amongst young women in Australia

AIHW 2014

Mental Illness in Australian Women

- Deliberate self-harm – females record higher age-adjusted rates of hospitalisation due to intentional self-harm than males across all age groups (10–14 to 60–64)

AIHW 2014

Perinatal Depression

- Perinatal depression – one in five mothers of children aged 24 months or less are diagnosed with depression.
- More than half of these mothers reported that their diagnosed depression was perinatal (that is, the depression was diagnosed between pregnancy and the child's first birthday).
- This represents an estimated 111,000 Australian mothers being diagnosed with depression, and 56,000 with perinatal depression annually.

AIHW 2014

Women and Mental Health

2X more women **attempt suicide** than men

2X as likely as men to develop **depression**

Anorexia and **Bulimia** are **3X** more common in women than men

2X as likely as men to suffer **anxiety disorders**

1/12 women will develop **alcohol dependence** during their lives

2X more likely than men to experience **Post Traumatic Stress Disorder**

The Cost of Mental Illness in Women

- The economic impact of depression/anxiety in women in Australia due to direct lost productivity is estimated to be $22 billion per year (ABS 2012 data)
- Add in costs of treatments, lost earnings, cost of loss of effective parenting of children, divorce, loss of care of elderly and other……

Gender and Mental Health

- Mental health (like physical health) is clearly gendered
- Men and women have different patterns of mental illness and other forms of mental distress and they are exposed to different risk factors and vulnerabilities
- A number of different theories have been proposed for the gender differences in the prevalence of mental health problems

Theories to Explain Gender Differences in Mental Illness

- Social theories
- Biological theories
- Psychological theories

Women and Mental Disorders

- **SOCIAL:** Violence, poverty, gender inequities in wages, power, social roles
- **BIOLOGY:** Hormone impacts, gender differences in drug metabolism systems, brain circuitry and genetic transmission
- **PSYCHOLOGY:** Psychiatric illnesses may present very differently in men and women because of gender differences in psychological responses and defences

GLOBAL SOCIAL IMPACTS ON WOMEN'S MENTAL HEALTH

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United States

Russia

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Domestic abuse in Russia

- 600,000 women victims of domestic abuse every year
- 14,000 die from injuries inflicted by husbands or partners each year

Source: Russian interior ministry estimates

Russian President Vladimir Putin has passed a controversial bill that reduces the penalty for domestic violence. Picture: Alexei Nikolsky, Sputnik, Kremlin Pool Photo via AP. Source:*AP*

RUSSIAN President Vladimir Putin has signed into law a controversial bill easing punishment for domestic violence, which critics say will make holding abusers accountable even more difficult.

Indian Politician, Babulal Gaur, Reveals His Thoughts On Rape: 'Sometimes It's Right, Sometimes It's Wrong'

MAIL TODAY VIA GETTY IMAGES

Just a week after the gang rape and murder of two teenagers, an Indian politician has said rape is "sometimes it's right, sometimes it's wrong."

The Huffington Post UK 6th June 2014

India has a sexual assault problem that only women can fix

August 27, 2018 8.45pm AEST

Public outrage followed the 2012 gang rape of a 23-year-old woman on a bus in Delhi, India. Here, demonstrators call for justice at the one-year anniversary of the incident. Reuters/Anindito Mukherjee

India is the most dangerous country for sexual violence against women, according to the Thomson Reuters Foundation 2018 survey.

Author

Nisha Bellinger

Sudan

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'True hell' of mass rape in Darfur revealed in report on Sudan

Rape by Sudanese forces in Darfur revealed in Human Rights Watch report as agency says UN and African Union should take urgent steps to protect civilians

Women in Tabit in Sudan's North Darfur state. Human Rights Watch says mass rape in the town could amount to crimes against humanity. Photograph: Mohamed Nureldin Abdallah/Reuters

The Guardian Feb 11th 2015

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How are we doing in Australia

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VIOLENCE AGAINST WOMEN: HOW AUSTRALIAN PSYCHIATRIC UNITS PERPETUATE VIOLENCE AGAINST VULNERABLE WOMEN

October 13, 2016 · by Jayashri Kulkarni · in Research & Technology

Since the 1960s, psychiatric inpatient units in many parts of the world have housed male and female patients together. The level of illicit drug and alcohol use in the inpatient population, both prior to and during hospitalisation, heightens the level of behavioural disinhibition in the inpatient population.

Embed from Getty Images

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Increasing rate of abuse of girls in Australia

- There is an increasing number of early – mid teenaged girls with incidences of maltreatment – sexual abuse, physical violence and/or neglect *
- The biological, psychological and social impact of this is long – lasting, with obesity, poor education attainment, health services engagement due to self harm and rage with resultant poor quality of life

*(ABS data 2011 v ABS data 1996)

Precocious Sexualisation

Toddlers & Tiaras
Contestant – Aged 4

Miley Cyrus – Aged 9

Early Sexualisation of Girls and Mental Illness

- Premature sexualisation is linked with serious mental health problems like eating disorders, low self-esteem and depression
- Sexualisation puts girls in danger. It contributes to exploitation and violence against girls and women. It increases sexism, sex bias, and sexist attitudes

Ref : Womensforum Australia 2013

Women and Mental Disorders

- BIOLOGY: Hormone impacts, gender differences in drug metabolism systems, brain circuitry and genetic transmission.
- PSYCHOLOGY: Psychiatric illnesses may present very differently in men and women because of gender differences in psychological responses and defences
- SOCIAL: Violence, poverty, gender inequities in wages, power, social roles

WOMEN'S MENTAL HEALTH

- Currently women's mental health is not a national priority.
- This is not good enough!
- Improving women's mental health is intimately tied to improving her well being + productivity, the next generations' outcomes and the mental health of her family & our community.


Risk Factors
Protective Mental Health Policy

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BIOLOGICAL IMPACTS ON WOMEN'S MENTAL HEALTH

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Hormones and the Brain

- Estrogens, progesterones, androgens – are all potent neurosteroids
- Significant evidence for modulation of dopamine, noradrenaline, serotonin, glutamate and acetylcholine by estradiol, progesterones and androgens
- Longstanding clinical / anecdotal evidence for biological hormone impact on mental state

Specific Mental Illnesses in Women

- Depression related to reproductive events:
  - PMS/PMDD
  - Depression and the OC Pill
  - Postnatal Depression
  - Perimenopausal Depression
- Borderline PD/ Complex Trauma Disorder
- Relapses of Psychosis related to estradiol fluctuations

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PMDD

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Premenstrual Dysphoric Disorder (PMDD)

- A real entity
- 80% of women have some challenge relating to menses, 40% have PMS,10-15% have PMDD
- Does not necessarily have a clear premenstrual pattern
- But has a cyclical onset with rapid onset and offset

PMDD TREATMENTS

- For severe PMDD (NOT PMS, not another psychiatric condition), vitamins, herbal treatments, lifestyle changes are ineffective
- Hormone treatments very important – suggest trying first line:
  - A) OCP – continuous. We favour “Zoely” – natural estradiol + nomegestrol acetate
  - B) OCP plus estradiol

PMDD

2nd Line treatments:

- SSRIs – use short half life drugs, less agitating ones – eg: citalopram, sertraline. Test with pharmacogenomic testing www.genesfx.com.au

3rd Line treatments:

- SSRI + estradiol
- SSRI + aldosterone

4th Line treatments:

- GnRh agonist drugs (eg: Synarel) + add back estradiol (chemical menopause)

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DEPRESSION & THE PILL

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Introduction

75% of Australian women report using a contraceptive medication at some time

Discontinuation of hormonal contraceptives due to mood side - effects is ***very common***!

Yusuf & Siedlecky (2007)
Sanders, Graham, Bass & Bancroft (2001)
Slade, Johnston, Oakley-Brown et al (2009)

Hormones and Mood

- Estrogen and progesterone affect many neurotransmitter systems involved in mood regulation

	5-HTT	5-HT_{1A}	5-HT_{2A}	MAO	D_2	β-Adrenergic	$GABA_A$	NMDA
Estradiol	↓	↓	↑	↓	↑	↑	↑ / ↓	↑
Progesterone				↑		↑	↑	

Dunn & Steiner (2000)

Currently, despite the pill being used worldwide by millions of women for over 50 years, we have no way of predicting which women are likely to experience adverse effects of OCs on mood, nor which OC formulations are more likely to be responsible

Sanders, Graham, Bass & Bancroft (2001)

Depression and The Oral Contraceptive Pill Studies

Jayashri Kulkarni

Emily Hayes, Sarah Metcalfe,

Roisin Worsley, Annabelle Warren,

Caroline Thew, Emmy Gavrilidis, Natalie Thomas, Gemma Sharp, Caroline Gurvich.

The Monash Alfred Psychiatry Research Centre

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Which "Pill" is best for mood?

From our studies (ongoing) and clinical practice:

- Low dose estradiol (20mcg) – worse for depression
- Drospirenone (Yaz,Yasmin) – worse for aggressive behaviours
- Norethisterone, levonorgestrel, medroxyprogesterone in OCs – not great for mood

Which "Pill" is best for mood? Cont'd

- Progesterone – only – worst of all for mood (especially depot provera or Implanon(etonogestrel)
- Multiphasic OCs worse for mood than monophasic OCs
- Best so far for mood is ZOELY (nomegestrol + 1.5mg oestradiol). But has weight gain and acne side effects
- **STILL WAITING FOR A GOOD OC FOR MOOD AND OTHER ADVERSE EFFECTS**
- **Read the SKOVLUND study**

(JAMA Psychiatry. 2016 Nov 1;73(11):1154-1162)

Perimenopausal Depression

Under recognised and underrated

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Perimenopausal Depression

- Very high incidence of first onset depression in perimenopause. Even higher relapse risk of depression in women with past history
- Overall depression rates increase up to sixteen times in 42-52 year old women
- Second highest completed suicide group – in Australia – women aged 45-52
- Declining / chaotic HPG axis function occurring from age 43-55. CNS changes first – up to 5 years before hot flushes, amenorrhoea

Perimenopausal Depression Symptoms

- Plummeting self – esteem
- Paranoid ideation
- Aggressive
- Disconnection
- No libido
- Irritable / agitated
- Weight gain
- Poor sleep (compounded by hot flushes)
- Memory / concentration changes
- Anxiety / Panic

Kulkarni et al. Translational Psychiatry (2018)8:123
DOI 10.1038/s41398-018-0172-0

Translational Psychiatry

ARTICLE Open Access

Development and validation of a new rating scale for perimenopausal depression —the Meno-D

Jayashri Kulkarni[1], Emorfia Gavrilidis[1], Abdul-Rahman Hudaib[1], Caitlin Bleeker[1], Roisin Worsley[1] and Caroline Gurvich[1]

Abstract

The menopause transition is a time when women experience an increased risk for new onset depression, as well as relapse of depression. While there are overlapping symptoms between major depression and depression during menopause, differences suggest 'perimenopausal depression' may be a unique subtype of depression associated with characteristic symptoms. There is currently no validated scale designed to measure perimenopausal depression. The aim of the current study was to develop and validate the 'Meno-D', a self-reporting or clinician rated questionnaire, designed to rate the severity of symptoms of perimenopausal depression. The development phase of the Meno-D involved literature review, clinical observation, and focus groups. A 12-item questionnaire was developed and clinically reviewed for face validity for content. The Meno-D was administered to women experiencing symptoms of perimenopausal depression as part of a larger baseline assessment battery. Validation involved confirmatory factor analysis (CFA). The development of the Meno-D resulted in 12 items. A total of 93 participants with perimenopausal depression were involved in the baseline assessments; 82 completed the Meno-D. Factor analysis identified five sub-scales of the Meno-D "somatic; cognitive; self; sleep; sexual" with high-internal consistency; discriminant validity and a good construct and convergent validity. The Meno-D provides a unique tool for clinicians and researchers to measure the presence of perimenopausal depression.

Introduction

Women have approximately twice the risk of developing depression or anxiety disorders compared to men[1,2]. The menopause transition is a time when women are at an increased risk for new onset depression, as well as relapse for women with a history of depression[3–6]. While there are many overlapping symptoms between major depressive disorder and depression occurring during the menopause transition, there are also key differences that indicate 'perimenopausal depression' may be a unique subtype of depression[3]. The diagnosis and quantification of perimenopausal depression requires a new rating scale to reflect the unique subset of symptoms. This study presents the development and validation of a novel scale specifically designed to measure the severity of perimenopausal depression symptoms.

The perimenopausal period refers to the interval immediately preceding menopause, when women transition from a reproductive to a non-reproductive state, until menopause, when menses have ceased for a period of at least 12 months. The perimenopausal period typically begins for women during their mid-to late 40s with a number of physical and mental health changes which continue for ~4–5 years before menopause is reached[7]. The Stages of Reproductive Aging Workshop (STRAW) criteria provide the gold standard for characterizing reproductive aging through reproductive stages and menopause[8]. The STRAW recommends that the late reproductive stage is accompanied with subtle endocrine changes that transition into a perimenopausal period that

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Aetiology of Perimenopausal Depression

- A subset of women seem to be predisposed to experience mood disturbances triggered by hormonal fluctuations
- This subset includes women with a history of mood disorders or of premenstrual and postnatal mood-related symptoms or a female family history of mood disorders related to hormone events
- Women with no previous history of mood disorders at all can develop severe perimenopausal depression de novo
- Not found with usual hormone lab investigations – this is brain estradiol fluctuation

Perimenopausal Depression Management

- Depression in middle aged – multifactorial
- Antidepressants or MHT? Usually both, but if possible better to start with MHT
- Sleep regulation
- Natural medicines
- Psychotherapy

Menopause Hormone Treatment

- Currently, the evidence base in terms of clinical trials conducted with menopausal hormone treatments in actual perimenopausal depression is limited
- MHT is useful in treating perimenopausal depression
- MHT Practice Suggestions: International Menopause Society (IMS) guidelines updated in 2016
- The MHT types that are available for use in perimenopausal depression treatment include – conjugated equine estrogen (CEE) or transdermal estradiol 75–100 mg/day or oral ethinylestradiol Micronized progesterone can be administered as a cyclic regimen

MHT Practice Suggestions

- International Menopause Society (IMS) guidelines updated in 2016
- The MHT types that are available for use in perimenopausal depression treatment include – conjugated equine estrogen (CEE) or transdermal estradiol 75–100 mg/day or oral ethinylestradiol
- Micronized progesterone can be administered as a cyclic regimen

The “Pill” for Perimenopausal Depression

- In early transition to menopause, the combined estrogen/progestogen contraceptive pills are useful treatments, although it is important to keep in mind that many COCs may be associated with increases in depression
- Zoely as a pill has less depression than other pills

Tibolone

- Tibolone is a synthetic steroid and has a mixed hormonal profile. Its estrogenic potency is about 1/50 of that of ethinyl-estradiol, its progestogenic potency is 1/8 that of norethisterone acetate and the androgenic potency is about 1/3 that of norethisterone. It has been proven to relieve climacteric symptoms and improve libido as well as assist in the management of perimenopausal anxiety and mild depression
- Adverse effects with tibolone is intermenstrual bleeding. but an advantage of tibolone treatment is that it does not cause increased breast density

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Tibolone improves depression in women through the menopause transition: A double-blind randomized controlled trial of adjunctive tibolone

Jayashri Kulkarni*, Emorfia Gavrilidis, Natalie Thomas, Abdul-Rahman Hudaih, Roisin Worsley, Caroline Thew, Caitlin Bleeker, Caroline Gurvich

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ABSTRACT

Background: Many women with no past psychiatric history experience severe mood symptoms for the first time in their life during the menopausal transition, with debilitating long-term consequences. Women with a history of depression can experience a relapse or worsening of symptoms during the menopause transition. Traditional antidepressants, SSRIs or SNRIs, are commonly prescribed as the first line response. However, such treatment has shown only small improvements with side effects. Hormone therapies directly targeting the perimenopausal fluctuations in reproductive hormonal systems such as tibolone, have significant potential to treat perimenopausal depression. Our study investigated the use of adjunctive tibolone, selective tissue estrogenic activity regulator, to treat de-novo or relapsing depression occurring during the menopause transition period.

Methods: Women who were going through the menopause transition with depressive symptoms were invited to participate in a double-blind, 12 week randomized control trial with two arms: tibolone (2.5 mg oral/day) or oral placebo (ACTRN12614000492). Forty-four women met inclusion/exclusion criteria; 22 were randomized to tibolone and 22 were randomized to oral placebo. Symptoms were measured with the 'Montgomery-Asberg depression rating scale' (MADRS) as the primary outcome measure. Latent growth curve analysis was used to assess the MADRS scores change over time.

Results: Participants in the tibolone group demonstrated a significant improvement in depression scores, as compared to the placebo group, without any significant side effects.

Limitations: This trial only monitored tibolone's effects over 12 weeks. Future research should be conducted over an extended timeframe and explore whether the benefits of tibolone extend to other symptoms of perimenopausal depression.

Conclusions: The use of hormone therapies such as tibolone provide exciting innovations for the treatment of depression during the menopause transition.

The menopause transition is a time of significant fluctuation and change in reproductive hormones. Adverse psychological symptoms, particularly depressive symptoms, are commonly reported during this period. The term "perimenopausal depression" has been utilized to describe the specific depressive symptomatology that can occur during the menopause transition (Parry, 2008; Steinberg et al., 2008), which appears to be a subtype of depression with a unique aetiology (Kulkarni, 2017). Women experiencing perimenopausal depression may respond differently to antidepressant medications as compared to women experiencing depression outside of the menopause transition (Kornstein et al., 2000a), that hormone treatments may be more effective for this group of women.

The perimenopausal period is defined as the time immediately prior to menopause, beginning with endocrine, biological and clinical changes, and ending the year after the final menstrual period and typically begins for women during their mid-to-late 40s (Brambilla et al., 1994a). Longitudinal epidemiological studies have shown that many women experience significant physical and mental health changes approximately 4–5 years before menopause is reached (Bromberger, 2006; Cohen et al., 2006). Although vasomotor symptoms such as hot flashes and night sweats occur in up to 70% of perimenopausal women (Brinton et al., 2015), the major reason that many women seek help during perimenopause is for depression and anxiety symptoms (Dennerstein et al., 1999). For many women, these symptoms impact significantly on their quality of life, social and personal well-being (Brambilla et al., 1994b).

Accumulating data indicates that the menopause transition is associated with an increased risk of depressed mood, for women with a

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http://dx.doi.org/10.1016/j.jad.2016.04.005
Received 6 December 2015; Received in revised form 26 February 2016; Accepted 6 April 2016
Available online 24 April 2016

MHT for Depression

- The risks and benefits of MHT differ for women during the menopause transition compared to those for older women. Bioidentical hormones are not recommended by the IMS because of standardization and dosing issues[1 SEP]

Treating Women with new Depression Related to Perimenopause

- Assess and monitor severity (including suicidality) – new doesn't mean less severe
- Be aware of SSRI agitation
- HT more acceptable to most women
- Natural therapies
- Psychotherapies – support but don't treat this depression
- Combinations of the above
- Address weight gain and physical health issues

Antidepressant Use – Depression in Perimenopause

- Commonly used to treat anxiety, depression, sleep problems, hot flushes
- SNRIs popular (low dose venlafaxine)
- Issues – discontinuity problems, blunting, aggression, problems with tachyphylaxis
- Match symptom with antidepressant eg: agitation worsened by fluoxetine
- Consider circadian rhythms restoration

New Approaches: Our Research

- Recognition of the condition
- Safe, shorter – term hormone treatment
- Different antidepressant approach (on/off)
- Physical health overview – tackle weight gain, wine consumption, lack of exercise
- Working with natural medicines too

Emma

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Emma

- Emma, now 26 – was raised by her single mother
- Her father left when Emma was 5
- She was sexually abused by her mother's boyfriend when she was aged 8 to age 14
- She told her mother who did not believe her
- Emma left home at age 16 and has a history of amphetamine abuse, alcohol abuse

Emma

- She cuts her arms and wrists and says this makes her feel “alive”
- Emma could not complete school and said she was unable to concentrate and has a “bad memory”
- She feels empty inside and often looks “dazed”
- Emma has angry outbursts over minor things

Emma

- Emma is very overweight
- She has made 11 suicide attempts
- Emma has had 4 admissions to psychiatry wards

Emma

Emma has a diagnosis of

“BORDERLINE PERSONALITY DISORDER”

What is Borderline Personality Disorder?

- The DSM 5 term is “Borderline Personality Disorder”
- What a useless term!!
- A better term is **COMPLEX POST TRAUMATIC STRESS DISORDER (ICD 11)**

Symptoms of BPD/CTD

- Deep feelings of insecurity
- Fear of abandonment and loss
- Rage & anger
- Fragile sense of self / feel fragmented
- Dissociation with stress
- Self-harm
- Persistent impulsiveness
- Confused, contradictory feelings

Symptoms of BPD/CTD

- May experience **anxiety** or **mood disorders**
- May experience **psychotic symptoms**
- Re-appearance of symptoms at **menopause**
- **THIS CONDITION IS COMPLEX, HARD TO DIAGNOSE. CONTAINS MANY SYMPTOMS THAT OCCUR IN OTHER CONDITIONS**

What Causes CTD/BPD?

85% of cases:

- Early Life Trauma (many types)
- Early Life Deprivation (loss of, disruption of primary care)
- Early Life Privation (no real primary care)

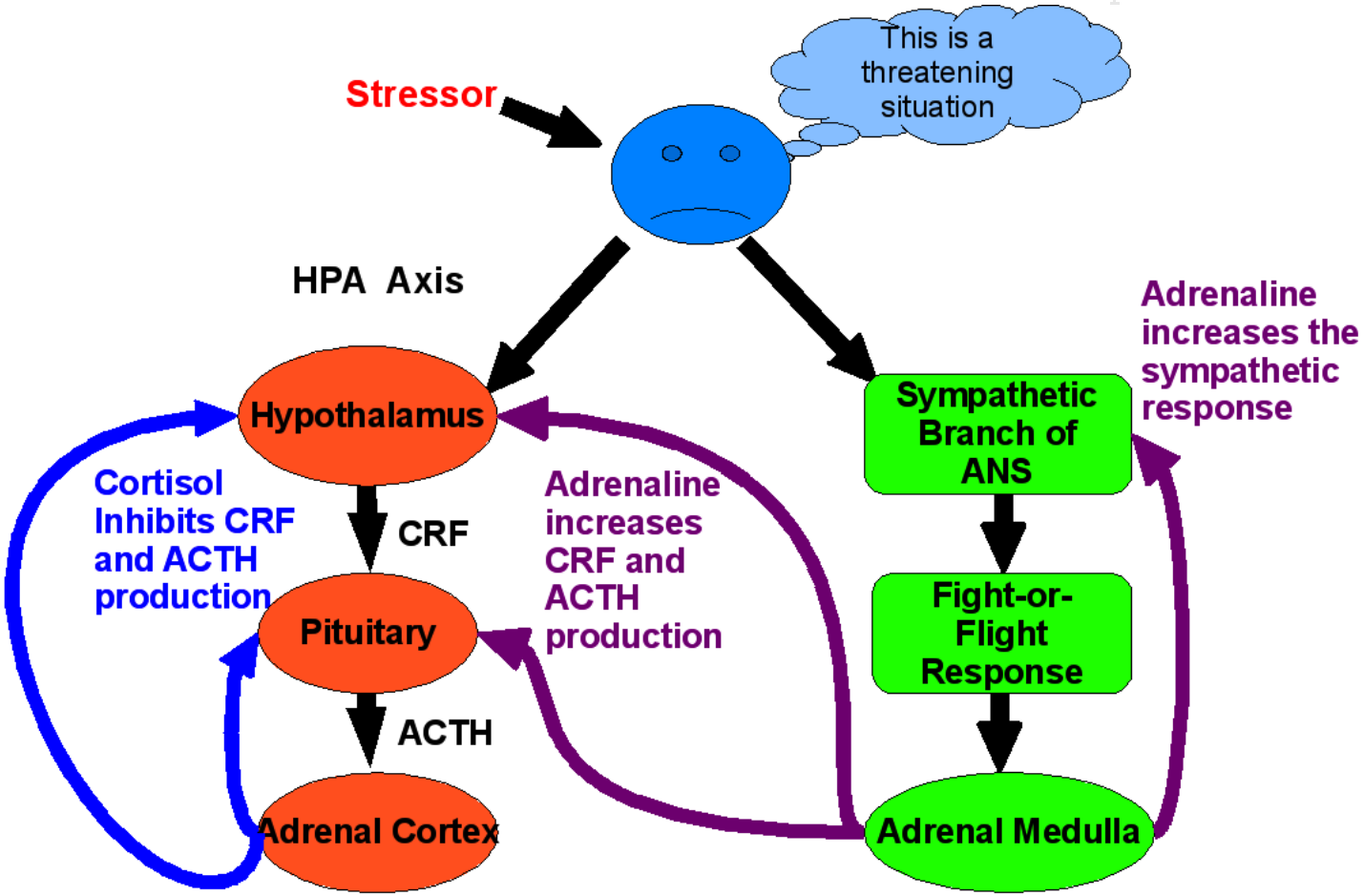
15% of Cases:

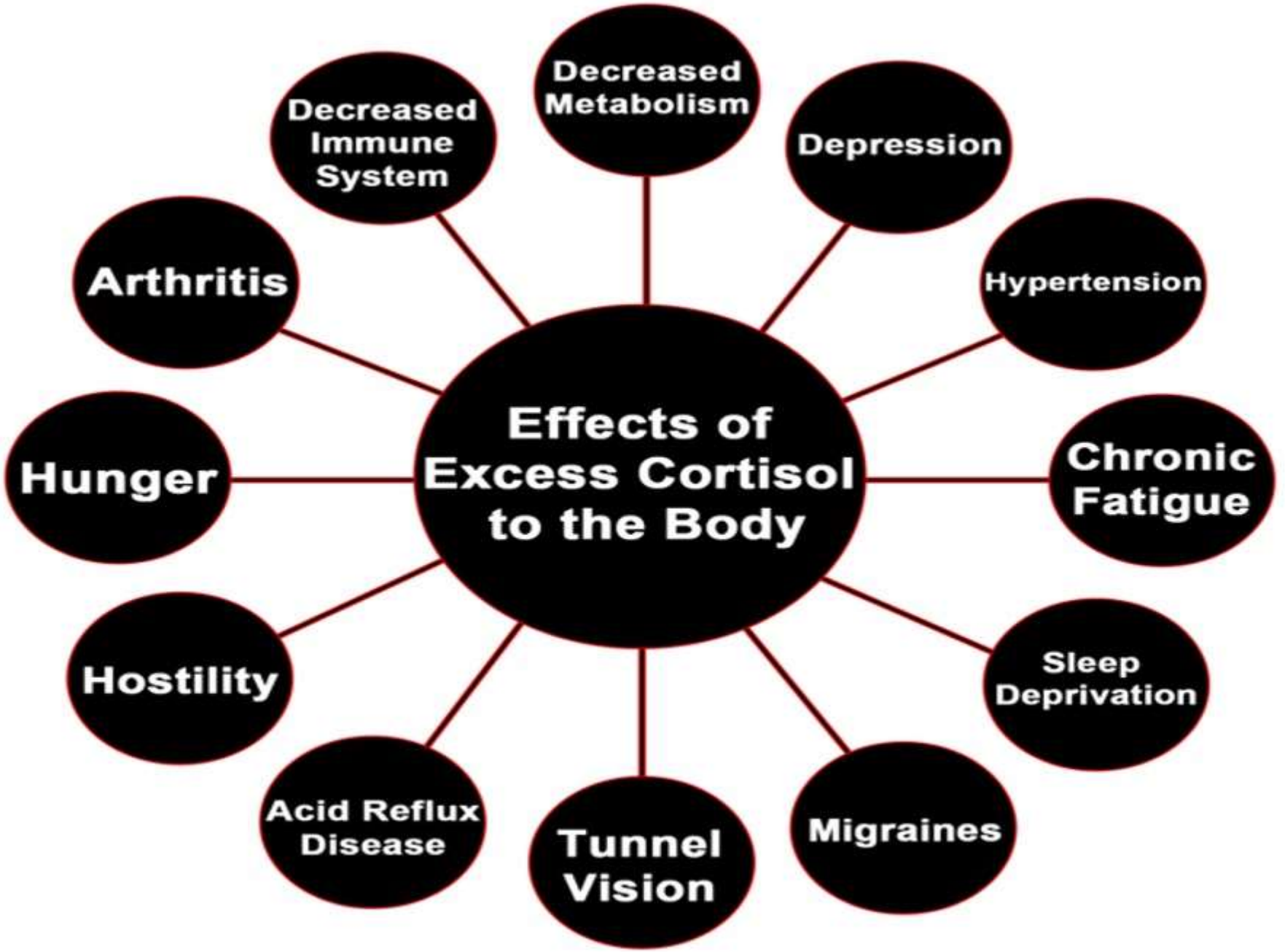
- ?Genetic factors

Many Biological Issues in Women with CTD/BPD

- Obesity
- Diabetes
- Infertility
- Abnormal menstrual cycles
- Chronic fatigue
- Fibromyalgia
- Increased susceptibility to infections

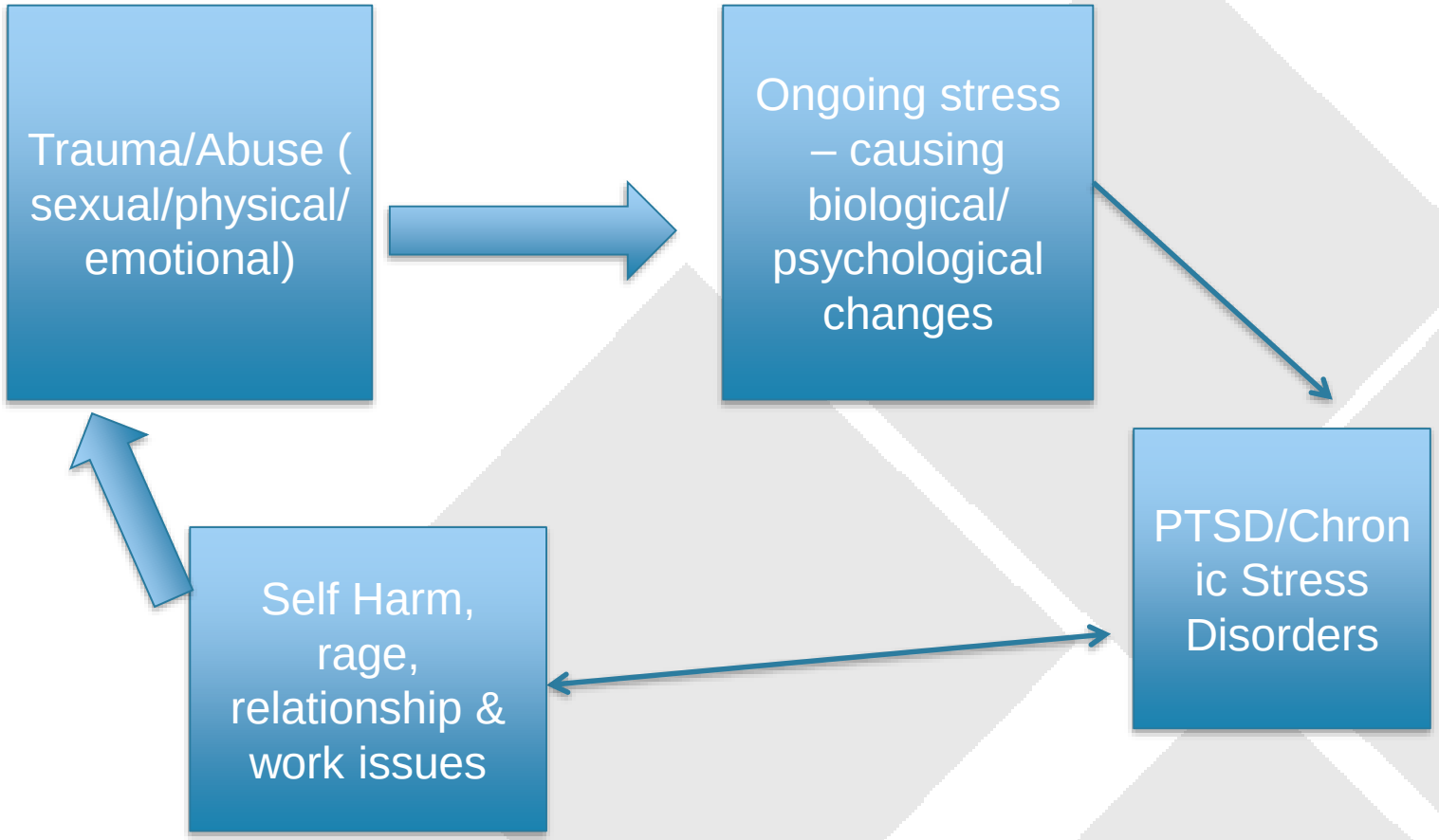
Biology of Stress Induced by Trauma





Cortisol - The Stress Hormone

Relationship between Abuse/Stress & CTD



Our Research in CTD

- New treatments being developed for people with CTD with NMDA receptor modulator
- Hormone treatments for women with CTD
- New clinical approach by linking trauma with biological changes, renaming the condition
- Special psychotherapy
- Education of health professionals, general public about CTD

Effect of the Glutamate NMDA Receptor Antagonist Memantine as Adjunctive Treatment in Borderline Personality Disorder: An Exploratory, Randomised, Double-Blind, Placebo-Controlled Trial

Jayashri Kulkarni, Natalie Thomas, Abdul-Rahman Hudaib, Emorfia Gavrilidis, Jasmin Grigg, Raelene Tan, Jacinta Cheng, et al.

CNS Drugs

ISSN 1172-7047

CNS Drugs
DOI 10.1007/s40263-018-0506-8

Springer

Some Other Current WMH Research

- Estrogen and “brain estrogen” treatment in women with schizophrenia
- Hormone treatment for Women with Bipolar Disorder
- Menopause & Anxiety
- Women’s safety in our inpatient wards
- Educating GPs and other clinicians on the assessment of Domestic Violence
- Brain stimulation treatment for women
- Many, many other projects in women’s mental health….

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WOMEN'S MENTAL HEALTH

WHERE TO FROM HERE?

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New Approaches Needed Now

- One size does not fit all!
- Specific mental health approaches **for women** urgently needed

An Integrated, Tailored Approach

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- We need to tackle the culture – to decrease violence, decrease drug and alcohol use, increase productivity for good mental and physical health for women and men
- Pursue Women's Health and Women's Mental Health agendas vigorously
- Provide new women focused treatments through more research
- Provide more advocacy
- Address safety, privacy and treatment access issues for women with mental ill health
- Continue with "White ribbon" programmes and more
- Pursue gender equality in pay, social responsibility and equity domains

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Women's Mental Health
Let's make it a national priority!

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